Catalytic conversion of glucose to 5-hydroxymethylfurfural as a potential biorenewable platform chemical

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Catalytic conversion of glucose to 5-hydroxymethylfurfural as a potential biorenewable platform chemical

by
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A dissertation submitted to the graduate faculty
in partial fulfillment of the requirements for the degree of

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ABSTRACT

The overall goal of the present work is to devise a catalyst system, in which novel catalyst and reactor configuration design will be synergistically performed on the dehydration of glucose. We have successfully demonstrated in the following chapters that MCl₃-type Lewis acids are effective catalyst to realize the efficient HMF production. Despite a number of reports on this strategy by us and other groups, a generalized frame to understand the intrinsic properties of employed Lewis acids and kinetic information relevant to processing development on this type of catalysts will also be explored in a systematic manner.

After extensively reviewing the challenges and opportunities of HMF production from sugars, we first report the catalytic conversion of glucose in high yields (62%) to HMF using a Lewis acid metal chloride (e.g., AlCl₃) and a Brønsted acid (HCl) in a biphasic reactor consisting of water and an alkylphenol compound (2-sec-butylphenol) as the organic phase. The conversion of glucose in the presence of Lewis and Brønsted acidity proceeds through a tandem pathway involving isomerization of glucose to fructose, followed by dehydration of fructose to HMF. The organic phase extracts 97% of the HMF produced, while both acid catalysts remain in the aqueous phase. Water-compatible lanthanide-based Lewis acids were further tested to be able to catalyze the reaction under near-neutral conditions (pH=5.5) and a moderately high yield of 42 mol% could be obtained. The combined catalytic system also showed effectiveness to convert
other polysaccharides to HMF. Furthermore, the aqueous phase was recycled and used for multiple times without significant loss of catalytic performance.

Further effort to understand the factors governing catalyst activities/selectivities was also undertaken. The glucose conversion kinetic profile was used to reflect the Lewis acid character of different metal ions. It was found that the pH value of the aqueous solution played an important role in controlling the Lewis activities. For the lanthanide chlorides, their Lewis acidity was comparable under the pH values studied (from 2.5 to 5.5). However, the Lewis acidity strength of other metal salts, such as aluminum chloride, showed dependence on the pH value of the solution. Activation energies with various Lewis acids were also calculated with both glucose and fructose to obtain more insight about the strength of the catalyst-substrate interaction as well as the dehydration reaction. The kinetic isotope effect with labeled glucose molecules was also studied to explore a more mechanistic understanding of the dehydration, which likely involves the 2-H atom of the glucose molecule in the transition state.

While understanding the Lewis acidities using homogeneous model catalysts can be insightful, the ultimate practice of catalyst/catalytic processes likely necessitates the development of heterogeneous catalysts. In this regard, a robust and sustainable catalyst preparation method pyrolyzing glucose and taurine in the presence of CNT to obtain a versatile solid acids has been demonstrated. Characterization and textual properties of the catalysts were probed through the utilization of TEM, SEM, TGA, XPS. Additionally, solid state nuclear magnetic resonance(ssNMR) spectroscopy has been exploited to
further elucidate the chemical nature of carbon species deposited on the surface of CNT. Al(OTf)_3 as a model Lewis acidic metal salt was successfully supported on sulfonic groups tethered CNTs and tested for C_6 sugar dehydration for the production of HMF in tetrahydrofuran(THF)/water solvent system with good recyclability.

In addition, an integrated catalytic pathway has also been demonstrated to utilize HMF-derived 1,2,6-hexanetriol as starting materials for the production of nylon 6,6 monomers-adipic acid and hexanediamine. To realize this goal, gold nanoparticle supported on both carbon and metal oxide based materials have been synthesized and tested for 1,6-hexanediol oxidation using molecular oxygen. On the other hand, homogeneous iodine-containing molecules have been exploited for the conversion of 1,6-hexanediol to adiponitrile, which can be subsequently hydrogenated to produce the desired diamine.
CHAPTER 1: GENERAL INTRODUCTION - CATALYTIC DEHYDRATION OF C₆ CARBOHYDRATES FOR THE PRODUCTION OF HYDROXYMETHYLFURFURAL (HMF) AS A VERSATILE PLATFORM CHEMICAL


Tianfu Wang, Michael W. Nolte and Brent H. Shanks

1.1 Introduction

1.1.1 Incorporation of Biomass into Conventional Fuel and Chemical Production: Alternative to Petroleum Feedstock

Throughout the 20th century, the carbon supply for the production of chemicals and fuels to support society’s needs has been deeply rooted in fossil carbon reserves. Through developing these feedstocks, numerous technological breakthroughs have occurred, such as the development of porous zeolitic materials for the refinery, the synthesis of unprecedented quantities of new synthetic materials with wide ranging applicability (e.g., nylon, carbon fiber, etc.), and the exploitation of petroleum-sourced chemicals for application in human health and nutritional applications to name a few. In conjunction with these technological advancements, the global population has experienced a growth to about 7 billion people while living standards have also improved significantly, which in turn has resulted in the accelerated depletion of fossil carbon reserves. Due to the rapidly expanding worldwide population, particularly in emerging countries, it is
projected that over the next two decades, the world energy consumption and petroleum demand will increase by over 30\%. Therefore, it is imperative that alternative carbon sources are developed to at least augment petroleum-sourced chemicals. Taking all these considerations into account, biomass exists as a unique and promising candidate, with potential for improved sustainability and biodegradability relative to its petroleum counterpart. In the United States alone, an estimated 1.3 billion tons of dry biomass is produced annually from either agriculture or forest waste.

Catalyst development faces a multitude of unique technical, economic, and logistical challenges to utilize biorenewable feedstocks. In contrast to the petroleum-based industries, where unfunctionalized alkanes are the primary starting material, a biorenewables industry will use a feedstock with extensive and diverse functionality derived from carbohydrates and lignin, which have excess oxygen relative to current chemical products. In order to use these compounds for chemicals, the excess functionality will need to be selectively removed to produce the same or similar molecules to those used in the petrochemical industry. New chemistries and novel catalytic systems, that may not be as thoroughly studied as those of the established petrochemical industry, need to be developed by the catalysis community to address the over-functionalization challenge in biorenewables conversion. Of particular interest are the dehydration and hydrogenolysis reactions, which can effectively reduce the oxygen content and can be applicable to various biorenewables. The complexity and diverse reactivity of biomass molecules necessitate the systematic development of appropriate approaches for different components in plant biomass.
1.1.2. Lignocellulosic Biomass

First generation biorenewable feedstocks generally refer to vegetable oil and starch/sucrose, from which biodiesel and ethanol, respectively, can be produced. However, concerns arise when these feedstocks are used because vegetable oil, sucrose and starch are also food resources. Moreover, the quantity that can be generated economically is rather limited relative to the total production of fuels and chemicals. Hence, they can only be qualified as a transitional solution to the overall energy and materials requirements needed by a growing world population. From the long-term perspective, second generation biorenewable feedstocks, which are typically derived from lignocellulose, are required to meet the renewable carbon demands.

Lignocellulose is the major component found in plant and algae biomass, and the estimated annual production of lignocellulosic biomass is $\approx 2 \times 10^{11}$ metric tons\textsuperscript{9,10}. Lignocellulose consists of three major fragments: cellulose, hemicellulose and lignin with its representative structure shown in Scheme 1. Depending on plant type, the relative portion of cellulose, hemicellulose and lignin found in the biomass is different. For example, in dried hardwoods, cellulose accounts for 40-45% by weight, hemicellulose is typically 24-40%, and lignin is 18-25%\textsuperscript{11}. In cornstover, the percentages are around 27-48%, 13-17%, 14-31%, respectively\textsuperscript{11}.

Cellulose is the most abundant biopolymer, consisting of D-glucose units connected via β-1,4 linkages. Unlike the α-1,4 linkages in starch, extensive hydrogen bonding exists in the cellulose structure, making hydrolysis difficult\textsuperscript{12}. Dilute acid hydrolysis and enzymatic hydrolysis are commonly used to liberate the monosaccharide glucose units\textsuperscript{13}. 
The acid hydrolysis step can present hurdles for subsequent conversion steps since the use of base is typically required to neutralize the excess acids. Quite often, side products, such as dehydration products of glucose, can be also found in the effluent. The presence of side products can be harmful for the microorganisms used in downstream fermentation steps\(^\text{14}\). Enzymatic hydrolysis, on the other hand, can suffer from low turnover rates, high cost associated with the need for large quantities of enzyme, and difficulty in catalyst separation from solution\(^\text{15}\).

Hemicellulose is composed of a mixture of several different types of carbohydrates including mainly xylose and arabinose\(^\text{16}\). These C\(_5\) sugars are not as easily fermentable as their C\(_6\) counterpart glucose, however recent literature articles have demonstrated that xylitol (hydrogenation product of xylose) and L-arabinose can serve as functional sugar additives or replacements for high-fructose corn syrup-derived foods and beverages\(^\text{17}\). It has been shown that the addition of 2-3wt\% of L-arabinose into sucrose can reduce glucose uptake by about 70\% while maintaining a similar sweetness level to sucrose. As a result, these C\(_5\) sugar derivatives can serve as a health food resource\(^\text{17}\). The utilization of biomass for high value food or pharmaceutical applications like these can greatly improve the comprehensive economics of lignocellulose conversion and facilitate the likelihood of process commercialization. The dehydration of C\(_5\) sugars can yield furfural, which is currently commercially produced as a platform chemical having applications ranging from solvents to resins and fuel additives\(^\text{18}\).

Lignin is a highly cross-linked phenolic polymer\(^\text{19}\) and the robust aromatic C-O-C ether bonds present throughout make it very difficult to deconstruct into monomeric
constitutes. Therefore, efficient methods to depolymerize lignin are still a major goal. On the other hand, its aromatic-based structure gives lignin a high heating value. Lignin can potentially be upgraded into transportation fuels by hydrogenation and/or hydrodeoxygenation. A study by Lercher and coworkers found a method to quantitatively depolymerize lignin to its monomeric constitutes using a combination of base (as a catalyst) and boric acid (as a capping agent). Later, the same group also reported that using a dual-function catalyst system, comprised of Pd/C and H₃PO₄, can be used to hydrogenate the monomer phenols in an aqueous media to form cycloalkanes, an ideal fuel. Dumesic et al. found in the processing steps to convert cellulose and hemicellulose to chemicals and fuels, a solvent derived from lignin is particularly interesting for use in biphasic reaction systems in which the organic phase is the lignin-based phenol and the aqueous layer is the reactive media containing the carbohydrates and catalyst. The in-situ produced furanics (5-hydroxymethylfurfural, furfural) or lactones (gamma-valerolactone, GVL) can be selectively extracted into the organic phase, making the process sustainable with both reactants and organic solvent being derived from lignocellulose.

Processes designed to convert the entire carbon supply into useful chemicals and fuels are preferred, in order to realize the economical utilization of lignocellulose. If one portion is not converted, significant amounts of waste will be generated that will necessitate appropriate handling.
1.1.3. Major Lignocellulose Conversion Routes

Various approaches have been studied in order to produce renewable fuels and chemicals from lignocellulosic biomass. Based on the temperature range under which the lignocellulose is processed and deconstructed, conversion routes can be classified into three major categories (Scheme 2). From low temperature to high temperature, these three pathways involve: (1) depolymerization into monomers, typically under 200 °C; (2) pyrolysis and liquefaction, roughly around 500 °C; (3) gasification, above 800 °C.

1.1.3.1. Depolymerization of Biomass into Monomers

When the monomers are obtained, subsequent chemical or biological catalysis can be performed to selectively convert these monomers to important platform chemicals. This approach can be advantageous because each fraction of the lignocellulose can be converted via processes specifically developed to operate efficiently for each particular component. However, one of the disadvantages of this tandem cascade approach is the costly pretreatment and depolymerization steps needed to liberate monomers of each fraction. Additionally, the multiple steps required during the process will also add to the cost. From a systems level, an effective and compatible network of conversion strategies and catalysts is necessary to improve the overall yield on a carbon basis for each monomer.

1.1.3.2. Fast Pyrolysis and Liquefaction

Fast pyrolysis and liquefaction are two common methods used to directly convert raw lignocellulose into a mixture of liquid intermediates. Pyrolysis refers to the rapid heating of biomass to 400-600°C under an inert atmosphere to yield bio-oil,
incondensable gases, and char\textsuperscript{27}. The composition of bio-oil is very complicated with possibly more than 300 compounds including a high content of water. As such, the separation of components represents a significant hurdle. Bio-oil can later be stabilized and upgraded to useful chemicals and fuels by strategies including esterification or ketonization among others\textsuperscript{28,29}. In order to address the issue of low selectivity, recent efforts by Huber et al. have explored catalytic fast pyrolysis for the production of aromatics and fuels\textsuperscript{30}. Liquefaction processes are conducted in the condensed phase under lower temperatures and higher pressures\textsuperscript{25}. Both pyrolysis and liquefaction produce a complex and unstable liquid product that can be further stabilized and upgraded to resemble conventional crude oil. However, due to its poor selectivity to any single chemical species and resultant separation difficulties, thermochemical methods have a higher feasibility for producing fuels rather than chemicals. The advantage in thermochemical conversion lies in the benefit, from a logistical perspective, of allowing the operation of a distributed infrastructure. Smaller, and more numerous, satellite pyrolysis or liquefaction facilities can be used to convert low density biomass into bio-oil, which can then be transported to a larger centralized processing/upgrading facility\textsuperscript{29}. Upgrading of such bio-oil has been extensively studied by Dumesic et al. and has been reviewed in several recent articles\textsuperscript{25,31}.

1.1.3.3. Gasification

Gasification of lignocellulose under temperatures above 800°C results in the formation of syngas, consisting of CO, CO\textsubscript{2}, H\textsubscript{2}O, and H\textsubscript{2}\textsuperscript{31,32}. Syngas can undergo conventional Fischer-Tropsch (FT) synthesis to produce hydrocarbons as liquid.
transportation fuels or be fed to the existing petrochemical infrastructure\textsuperscript{33}. Syngas can also be converted to methanol, which can be used to make hydrocarbons and olefins for the polymer industry\textsuperscript{34}. These large-scale, technically mature strategies can produce fuels and chemicals that are compatible with the current infrastructure, but the disadvantage of this pathway is that the production of hydrocarbons and methanol from biomass remains relatively expensive and requires a large capital investment.

Overall, these three major strategies to convert lignocellulose have their own advantages and disadvantages. According to the speciation of biomass and targeted molecules, different routes (or combination of routes) may be devised to best suit the biomass stream of interest. The economical production of chemicals and fuels will depend on the selectivities of the catalytic conversion process. In general, the concept of producing platform chemical intermediates that can be subsequently converted to a range of products is particularly interesting.

The current review will focus on the production of the platform chemical 5-hydroxymethylfurfural (HMF). The C\textsubscript{6} sugar feedstock can be derived from the depolymerization of cellulose after it has been separated from lignocellulose (Section 1.3.1.). Other interesting platform chemicals have been discussed, but are beyond the scope of this review.\textsuperscript{20, 25, 31}

1.2. HMF as a Platform Chemical

HMF (Scheme 3) is a heterocyclic furanic molecule substituted in 2,5-position with hydroxide and aldehyde functionalities. Because of its unique chemical structure, the
effort in utilizing HMF as a starting point for the synthesis of functional replacement or
direct replacement alternatives to the current commodity chemicals mainly results from
three molecular attributes. First, HMF is an α,ω-bifunctional molecule with substituents
in both the 2 and 5 positions, so it can be either oxidized to a dicarboxylic acid or reduced
to a diol. Both of which can be used for the synthesis of polymers. Second, HMF is a
relatively unsaturated aromatic compound and can be upgraded to fuel molecules via
hydrogenation. Finally, the heterocyclic structure of furans can be found in an array of
biologically active molecules with pharmaceutical applications. The current review will
focus on the first two applications and the last topic can be found in a review published
recently35.

1.2.1. HMF Derivatives as Monomers for Polymeric Materials

1.2.1.1. HMF to Furandicarboxylic Acid (FDCA)

It has been shown that PEF (polyethylene furanoate), made from FDCA and
ethylene glycol, has similar physical, mechanical and chemical properties to the
petroleum-based analog, PET (polyethylene terephthalate)36,37. FDCA is produced
through the oxidation of HMF, which has been reported for a number of homogeneous
and heterogeneous systems. In a study by Corma and co-workers, 99 mol% yield of
FDCA was achieved using Au/CeO$_2$ and Au/TiO$_2$ as catalysts, in aqueous media$^{38}$.
Gorbanev et al. systematically studied the effect of added bases and oxygen pressure on
the HMF oxidation reactions with Au/ TiO$_2$ under ambient temperature at 30°C$^{39}$. They
concluded the bases are required for such conversion and reported a 71 mol% yield of
FDCA at full conversion of HMF. In order to improve the activity and selectivity as well
as stability of the catalysts, bimetallic catalysts have also been reported for HMF oxidation. Pasini et al. reported the bimetallic gold-copper on TiO$_2$, in which a yield of 90–99% of FDCA was obtained at 95°C for 4h$^{40}$. In a study published by Abu-Omar and co-workers, a modification of a homogenous oxidation system, consisting of bimetallic zinc and cobalt bromides and acetic acid, gave greater than a 60mol % yield with 1 atm oxygen$^{41}$. Davis and co-workers used supported precious metal catalysts (Pt/C, Pd/C and Au/TiO2) under high pH conditions with molecular oxygen in an aqueous media leading to HMF being quantitatively converted FDCA in high yields. For the Pt/C system, about an 80 mol% FDCA yield was obtained$^{42}$. A plausible reaction mechanism and pathway has been proposed by the same research group (Scheme 4)$^{43}$. One of the disadvantages of these systems is that they need the addition of excess amounts of base. To address this problem, Abu-Omar and co-workers recently reported that 79 mol% FDCA can be achieved with an Fe$^{III}$-porphyrin complex supported on porous carbon materials without the need to add a base$^{44}$.

1.2.1.2. Diols from HMF

In addition to work reported for the oxidation of HMF to produce diacids, interest in converting HMF to diols has also been examined. Alamillo and co-workers reported in their study, dihydroxymethyltetrahydrofuran (DHMTHF) can be obtained in as high as ~90% yield by using a γ-alumina supported ruthenium catalyst to catalyze the hydrogenation starting with HMF$^{45}$. DHMTHF can be used as a monomer for polymer synthesis, or other applications. Using copper chromite as a catalyst for HMF
hydrogenation can be advantageous when the hydrogenation is preferred to proceed without saturating the furan ring\textsuperscript{46}.

1.2.2. Fuel Molecules From HMF

1.2.2.1. Furanic Compounds

In the past decade, etherification of HMF to 5-alkoxymethylfurfural ethers and hydrogenolysis of HMF (to form dimethylfuran, DMF) have been proposed for producing liquid transportation fuels (Scheme 5). In a report by Bell and co-workers, in which an alcohol is used as both reaction media and reactant, HMF can undergo acid catalyzed etherification to form furfural ethers\textsuperscript{47}. When Pt/C is used as the catalyst in the reaction mixture, reductive etherification also occurs, resulting in furfural di-ethers. These ether molecules are good candidates as liquid fuels with high heating values. Kraus et al. reported that in a binary system of sulfonic-functionalized ionic liquids and hexane, fructose could be directly converted to 5-alkoxymethylfurfural ethers with yields of greater than 50 mol\%. This reactive media can be recycled and the authors showed that the 5-alkoxymethylfurfural ethers yields didn’t drop significantly over five consecutive runs\textsuperscript{48}. Tsapatsis and co-workers used glucose as a feedstock directly, with a combined catalyst system involving Sn-Beta zeolite, a Lewis acid catalyst, and Amberlyst 131, a Brønsted acid. Glucose was hypothesized to undergo isomerization to fructose followed by dehydration/etherification to produce 5-alkoxymethylfurfural ethers with yields of 31 mol\%\textsuperscript{49}.

Amongst all the hydrogenation catalysts, copper has been shown to preferentially perform C-O bond hydrogenolysis over C-C bonds and thus can minimize aromatic
hydrogenation. Because of this, numerous copper-based catalysts have been reported to selectively hydrogenate HMF to DMF as an attractive fuel additive. In 2007, Román-Leshkov et al. reported HMF can undergo selective hydrogenolysis over copper-ruthenium catalysts in butanol solvent, yielding over 70 mol% DMF. Another study by Shanks and co-workers focused on the elucidation of the active speciation of copper in copper-chromite catalysts and their activity on C-O hydrogenolysis with furanic model compounds. Chidambaram et al. reported in their study glucose can be directly converted to DMF in a two-step, “one-pot” manner in an ionic liquid/acetonitrile mixed solvent. While almost quantitative yield of HMF from glucose was observed, less success was achieved in the second-step hydrogenolysis to DMF (with 15 mol% yield on Pd/C catalyst).

1.2.2.2. Liquid Alkanes

Dumesic and co-workers devised synthesis routes for C\textsubscript{9}, C\textsubscript{12} and C\textsubscript{15} alkanes using HMF and acetone as starting materials through a two-step condensation/hydrogenation and dehydration pathway. If a 1:1 HMF to acetone ratio was used, the aldol condensation gave a C\textsubscript{9} species, which can undergo a second-step hydrogenation/dehydration to form C\textsubscript{9} alkanes. Similarly, C\textsubscript{12} and C\textsubscript{15} alkanes can be produced using self-condensation of HMF resulting from use of a 2:1 HMF to acetone ratio. Although the economics of this pathway will rely on the high yield of HMF produced from lignocellulose feedstock and inexpensive hydrogen, this process clearly provides an alternative to produce liquid alkanes directly from cellulose-derived glucose.
The base catalyzed aldol condensation method to upgrade HMF to alkanes later has been extended to the biphasic system\textsuperscript{53} and solid bases\textsuperscript{54}. In the first case, Dumesic and co-workers reported a biphasic system where the aldol condensates were continuously extracted from the basic aqueous phase to prevent degradation. In the later case, Shen et al. examined the aldol condensation reaction between furfural and acetone over several solid base catalysts: MgO–ZrO\textsubscript{2}, NaY and nitrogen-substituted NaY at 120 °C. Their results showed MgO–ZrO\textsubscript{2} to be the most selective catalyst with almost 100% selectivity for moderate conversions (~50%). Recently reported work by Corma et al.\textsuperscript{55} and Yang et al.\textsuperscript{56} have used similar aldol-type strategies to obtain diesel range liquid alkanes from HMF or furfural.

In general, HMF is a versatile platform chemical, which can be converted to a broad array of fuel and chemical products. While the promise of using HMF is quite significant, the economical production of HMF at large scale is the major obstacle in unleashing the great potential of this platform chemical. Understanding the chemistry of carbohydrate dehydration to HMF is key providing insights into the proper catalyst design principles, which can then be coupled with reactor configuration and process optimization to improve the efficiency of the transformation.

1.3. Hexose Dehydration Mechanism

HMF is a triple dehydration product of hexoses (Scheme 6) with both glucose and fructose explored as feedstocks. The dehydration reaction has been catalyzed by both homogeneous and heterogeneous catalysts in aqueous, organic, and, most recently, ionic liquid media. A number of excellent review articles have been dedicated to the
production of HMF with several recent ones including, HMF and furfural synthesis work summarized by Hu et al.\textsuperscript{57}, mechanistic aspects of C\textsubscript{6} sugar conversion to HMF by Qian\textsuperscript{58}, heterogeneous catalyst systems for both HMF and furfural production by Karinen and co-workers\textsuperscript{59}, and HMF production using ionic liquids as solvents by Stahlberg et al.\textsuperscript{60} and Zakrzewska et al.\textsuperscript{10} Most recently, a published review article by Van Putten et al.\textsuperscript{35} has updated the current pilot and pre-commercial HMF production status and their applications. In the present review, we first briefly review the current hypothesis about hexose dehydration and then discuss fructose and glucose dehydration, before reviewing recent progress made in integrating glucose/fructose isomerization and subsequent dehydration to produce HMF.

No definitive conclusion has been made on the reaction mechanism for hexose dehydration in the literature. The hexose dehydration reaction to form HMF is generally accompanied by numerous other side reactions, which lead to the generation of humins and organic acids\textsuperscript{61, 62}. In addition, other molecules produced during hexose dehydration, particularly organic acids such as levulinic (LA) and formic acid, can self-catalyze the dehydration of hexose\textsuperscript{61}. Other factors thought to be important are solvent type, temperature, and catalysts\textsuperscript{63, 64}. Several mechanisms have been proposed for hexose dehydration and, in general, can be divided into pathways involving cyclic\textsuperscript{58, 63-66} or acyclic intermediates\textsuperscript{67, 68} (Scheme 7). Most of these studies were carried out with fructose in aqueous media.

In one study supporting the cyclic mechanism, Amarasekara et al. reported that the anomeric composition of D-fructose altered when heated to 150 °C with an increase in
the α-furanose form relative to the β-pyranose tautomer. Using $^1\text{H}$ and $^{13}\text{C}$ NMR spectra, they identified the key intermediate (4R,5R)-4-hydroxy-5-hydroxymethyl-4,5-dihydrofuran-2-carbaldehyde when using dimethylsulfoxide (DMSO) as the solvent, indicating the reaction proceed via a cyclic intermediate. In another combined experimental and computational study by Antal et al., fructose conversion was examined with mineral acids as the catalyst. Reaction kinetics was measured by monitoring the temporal composition of key products such as HMF, furfural, and levulinic acid. The authors found the cyclic pathway was more likely to account for HMF formation by observing a rapid kinetic profile when using 2,5-anhydro-d-mannose (an intermediate in the hypothesized cyclic pathway) as the reactant. The authors also performed the reaction in deuterium oxide (D$_2$O) and the lack of C-D bonds in the final HMF molecules contradicted the acyclic mechanism where keto-enol tautomerism will otherwise incorporate a D atom into the formed HMF. In 2011, Assary et al. examined the energetics of assumed intermediates of fructose dehydration using high-level quantum chemical methods. They found the acidity of the solution was essential to lower the activation energy barrier by proceeding via protonated intermediates. The calculated activation barrier at neutral conditions at 298 K was found to be as large as 74 kcal/mol, making the transformation under this condition very unfavorable. However, the cyclic forms of intermediates formed by combined protonation and hydrogen transfer can lower the activation barriers, facilitating fructose to HMF transformation.

Alternative mechanisms for HMF formation also involve an acyclic pathway, in which a 1,2-enediol has been suggested as an intermediate. Moreau et al. studied
fructose conversion using H-mordenites as a solid catalyst in aqueous media. Based on the detected formation of other hexoses like mannose and glucose, they suggested that fructose first isomerized to glucose and mannose via a 1,2-enediol. This hypothesis can also explain the observation of furfural and hydroxyacetylfuran, which have been postulated through their proposed reaction scheme. Unfortunately, no spectroscopic or labeling experiments were performed to confirm this hypothesis. Work by Qian et al. employed ab initio calculations to study the possible pathways of both C₆ and C₅ sugars and they concluded the rate-limiting step of the transformation from hexose to HMF is the protonation of the hydroxyl group and suggested the reaction proceeded via the acyclic pathway. Extensive research and mechanistic studies have also been conducted on C₅ sugar dehydration, which can be analogous to work done on C₆ sugar and provide further information about the transformation.

While the more abundant glucose is a preferred feedstock over fructose for HMF production, the rate of glucose conversion and selectivity to HMF are both lower than with fructose. The explanation for this observation is attributed to the fact that the cyclic furanose tautomer and the pyranose form of fructose co-exist in water. This leads to superior reactivity and HMF selectivity for fructose relative to glucose, which exists in aqueous solution with the pyranose form as the prevalent tautomer. The observed slower kinetics of glucose conversion relative to fructose also supports the cyclic mechanism for fructose dehydration to HMF, which hypothesizes a pathway involving the furanose form as an intermediate. To develop an efficient glucose to HMF conversion process, an effective method is needed that easily integrates glucose isomerization to fructose and
subsequent fructose dehydration to HMF. However, several considerations should be taken into account for the choice of glucose/fructose isomerization catalysts so as to be compatible with the Brønsted acid catalyst needed for fructose dehydration. Traditional glucose isomerization catalysts are bases or enzymes\textsuperscript{74, 75}, but these are not generally suitable for integration due to the base will neutralizing the Brønsted acid, and because enzyme activity and stability can be adversely affected in strongly acidic conditions. New catalysts that can function under the prerequisite condition need to be developed and in the past several years, systems such as CrCl\textsubscript{x}/ionic liquid, Lewis acidic zeolites and MCl\textsubscript{x} in water have achieved significant progress with relatively high HMF yields (>60 mol% directly from glucose). The common point of these three systems is the use of a Lewis acid for glucose isomerization to fructose in combination with a Brønsted acid for fructose dehydration to HMF.

In 2007, Zhao et al. reported the use of sugar-solubilizing 1-ethyl-3-methylimidazolium chloride, [EMIM]Cl, as a solvent, where fructose can be converted to HMF in yields of 80 mol% with 18 mol% H\textsubscript{2}SO\textsubscript{4} (relative to fructose) as a catalyst at 80°C\textsuperscript{76}. Glucose conversion was also studied and CrCl\textsubscript{x} Lewis acidic salts were identified as the most effective catalyst to obtain high yields of HMF (68 mol% to 70 mol%). Using NMR spectroscopy, the authors proposed the role of CrCl\textsubscript{x} in catalyzing glucose conversion (Scheme 8). They ascribed the activity of CrCl\textsubscript{x} to the interaction between glucose and CrCl\textsubscript{x} which leads to: (1) rapid mutarotation of glucose generating an equilibrium mixture of α- and β-anomers, and (2) isomerization of glucose to fructose via a formal hydride transfer from C-2 position to C-1 position through a [EMIM] mediated
enediol intermediate. Later in 2010, Pidko and co-workers proposed a different mechanism for glucose isomerization with Cr$^{2+}$ catalyst in [EMIM]Cl, based on data obtained from kinetic experiments, in situ X-ray absorption spectroscopy (XAS) and density functional theory (DFT). They concluded that a single Cr center was responsible for the equilibrium between the open and closed form of glucose. In contrast to [CrCl$_3$]$^-$ proposed by Zhao et al., Pidko et al. suggested a mechanism for glucose/fructose isomerization involving the formation of a transient binuclear complex between two Cr$^{2+}$ centers, analogous to the active site of hexose isomerase enzymes.

Another breakthrough was made by Davis et al. in 2010. They found a Sn-beta solid Lewis acid zeolite can isomerize glucose to fructose with high activity in water under both neutral and acidic conditions. The performance of the catalyst under acidic conditions opened up new opportunities for the facile integration of the isomerization step with the Brønsted acid-catalyzed fructose dehydration. Indeed, the same group later reported that using Sn-beta and HCl in a biphasic system, glucose can be directly converted to HMF with over 70 mol% selectivities. The mechanism of the isomerization has been studied using isotopic labeling experiments (D and $^{13}$C) and NMR spectroscopy. A hydride transfer mechanism has been suggested by the experimental results (Scheme 9). Kinetic experiments performed on two forms of glucose (one protonated and one deuterated at the C-2 position) to compare initial reaction rate displayed a kinetic isotope effect of 1.98, suggesting the proton at the C-2 position was involved in the rate-limiting step. Mass spectroscopy proved the prevalent C-D
incorporation in the product fructose, supporting the hydride transfer mechanism. In addition, $^1$H and $^{13}$C NMR data were in agreement with the proposed mechanism.

In addition to the above mentioned work using heterogeneous Sn-beta as the isomerization catalyst, Shanks and co-workers $^{81,82}$, Abu-Omar and co-workers $^{83,84}$, and Vlachos and co-workers $^{85,86}$ have been focusing on using homogeneous Lewis acidic metal chloride salts (e.g., AlCl$_3$, CrCl$_3$, YbCl$_3$) in combination with a Brønsted acid (HCl) to perform the isomerization/dehydration reaction. These reactions were carried out in biphasic systems and high HMF yields (~60 mol%) were obtained directly from glucose, with fructose being observed as an intermediate. Although more kinetic and mechanistic work is required to understand the reaction network, the authors proposed a similar hydride mechanism for the glucose/fructose isomerization.

1.4. Fructose Dehydration

The highest reported yields of HMF from hexoses use fructose as the starting reactant. The fructose dehydration reaction has been carried out using homogeneous and heterogeneous catalysts in monophasic systems and biphasic systems, as well as in ionic liquid solutions. Representative literature articles will be reviewed looking at each of the three solvent systems individually. Tables 1-3 summarize the results of fructose dehydration in these systems.

1.4.1 Fructose Dehydration in Monophasic Systems

In 1977, Kuster et al. developed analytical procedures for the quantification of fructose and its dehydration products $^{87}$. The procedures were used in a series of articles to find the effect of catalyst concentration, water concentration, and pH$^{88,90}$ on
dehydration rate and product yields. Using a reaction temperature of 95°C, ambient pressure, and higher acid concentration (2 M HCl), gave the highest yields of HMF in the study, ~30%, at a conversion of ~75%. In the next set of experiments, polyethyleneglycol-600 (PG-600) was added as a diluent. The highest PG-600 concentration used, 70% PG-600, gave the maximum yield of HMF at ~70% and ~90% conversion. In the final study, pH was controlled using the addition of formic acid. It should be noted that in this final set of experiments, the reaction conditions used were 175°C and 50 atm. The maximum yields of HMF were obtained at pH of 2.7-3.0 where yield was ~55% at ~70% conversion after 60-90 minutes. When the pH was not controlled, it was found that during reaction the pH decreased due to the formation of acids. For example, if no acid catalyst was initially added, the pH was measured to have decreased from 7.0 to 3.2.

A few years later, Nakamura and Morikawa used a strongly acidic ion-exchange resin, Diaion PK-216, in DMSO. At 80°C, a yield of 30% was obtained after 40 min. The yield increased to 90% for a reaction time of 500 min. Nakamura and Morikawa also used an Amberlite IR-118 resin at 60°C for the continuous dehydration of fructose and were able to achieve yields of 80-95% for reaction times up to 900 hours. Fructose was also dehydrated in pure DMSO without a catalyst by Musau and Munavu. In a 1:8.5 fructose:DMSO solution at 150°C, an HMF yield of up to 92% was obtained.

Van Dam et al. examined polyethylene glycol as a cosolvent with DMSO to increase the yield of HMF from fructose. Using 0.5 M fructose and 1 M p-toluenesulfonic acid
at 88°C and a 300 minute reaction time, the HMF yield increased from ~20% with no cosolvent (~65% conversion) to ~30% with 50 vol% PEG-200 and up to ~45% with 50 vol% PEG-4000. Interestingly, HMF yield decreased to <5% with the addition of 50 vol% ethylene glycol. The conversion of fructose with an added cosolvent was >90% for each of the three types of ethylene glycol. Van Dam et al. also experimented with changes in initial fructose concentration, acidity, and the addition of metal salts, but the effects on HMF yield were less pronounced when compared with a cosolvent addition.

Vinke and van Bekkum used activated carbon to adsorb HMF once it was produced to limit the rehydration to LA. Two different systems were used in the work; first, a one-pot reactor with the catalyst and adsorbent, and second, a batch reactor with continuous adsorption using separate catalyst and adsorbent beds. In the one-pot reactor, 9 g of fructose, 20 g of activated carbon, and 40 g of acidic ion-exchange catalyst (or an equivalent amount of HCl in 50 mL of water for homogeneously catalyzed reactions) were mixed in 150 mL of water. For continuous adsorption, a fructose solution was circulated between the catalyst column and then the adsorbent column. In both cases, reactions were carried out at 90°C, and in the continuous system, the adsorption column was operated at 25°C. In both systems, the maximum yield achieved was ~50% with an HMF selectivity of ~60-65%.

Carlini et al. used a solid acid niobium catalyst (niobic acid or niobium phosphate) in an aqueous environment at 100°C. HMF selectivity was high (> 90%) at low conversions (< 30%). When the reaction time was increased, fructose conversion increased while the HMF selectivity dramatically decreased. In a separate study, a range
of different metal-vanadyl phosphate catalysts were used at a slightly lower temperature, 80°C\textsuperscript{96}. In most instances, HMF selectivity was \textasciitilde 80-95\% and fructose conversion was \textasciitilde 45-65\%. In contrast, though, the decrease in HMF selectivity at longer reaction times was not as dramatic as with the niobium catalysts. Carniti et al. also used niobic acid and niobium phosphate as catalysts, but in a flow reactor\textsuperscript{97}. With a temperature between 90-110°C, there was an increasing trend between selectivity and conversion, with the maximum reported being a selectivity of 35\% at \textasciitilde 75\% conversion. However, catalyst deactivation was present in both systems. After 24 hours on stream, fructose conversion was \textasciitilde 60\% for niobium phosphate and \textasciitilde 40\% for niobic acid. The conversion decreased to \textlt 20\% for both catalysts after 200 hours on stream.

Watanabe et al. examined TiO\textsubscript{2} and ZrO\textsubscript{2} metal oxides in hot compressed water for glucose and fructose dehydration\textsuperscript{98}. From fructose, HMF yield was \textasciitilde 20\% with TiO\textsubscript{2} and \textasciitilde 15\% with ZrO\textsubscript{2}, with conversions being 90-100\% for each case. The reaction conditions were as follows: 200°C temperature, 25 bar Ar, and a 5 minute reaction time. Benvenuti et al. used different heterogeneous Ti and Zr phosphate catalysts\textsuperscript{99}. At 100°C, an aqueous solution of 6 wt\% fructose was converted with a cubic zirconium pyrophosphate (C-ZrP\textsubscript{2}O\textsubscript{7}) catalyst giving an HMF selectivity of 99.8\% (44.4 \% conversion) after 30 minutes. For longer reaction times the selectivity dropped to 86\% after 1 hour (52.2\% conversion) and to 82.1\% after 2 hours (52.8\% conversion). The Ti phosphate catalysts gave selectivities of 96-98\% at conversions of 25-35\% after 30 minutes. The authors concluded the both Lewis acid and Brønstead acid sites were active in the reaction, and as the Lewis acid site strength was increased the HMF yield in
Dutta et al. used microwave heating and a TiO$_2$ catalyst to obtain up to a 54% yield in DMSO at 140°C with 300 W of microwave power for 5 minutes$^{100}$. Lower yields were afforded in water, water:MIBK, and acetonitrile systems, and with decreased microwave power.

Qi et al. used an ion-exchange resin in an acetone-water mixture with microwave heating$^{101}$. The microwave irradiation heated the 5 g reaction mixture to 150°C within 30 sec. After ten minutes at reaction temperature in an 85:15 (w/w) acetone-water mixture, fructose conversion was 94% with 73.4% HMF selectivity. Decreasing the amount of acetone required increasing reaction times to reach comparable fructose conversions.

Bicker et al. also used acetone-water mixtures but at sub- and supercritical conditions (180-300°C, 50-300 bar)$^{102}$. Using sulfuric acid (10 mM) as a catalyst at 180°C and 200 bar, the highest yield for HMF was obtained in 90:10 acetone:water where the selectivity was ~75% at ~90% conversion.

Li et al. experimented with acetic acid and formic acid as catalysts in high temperature liquid water$^{103}$. The temperature was varied between 180°C and 220°C and without a catalyst HMF yield was ~50% at nearly full conversion. When either acetic acid or formic acid were added at 10.8 mg/mL, the yield increased to ~60% at 100% conversion. Their work suggested acetic acid may promote the dehydration of fructose to HMF, while having little influence on the rehydration of HMF to levulinic acid, whereas formic acid appeared to catalyze both steps.

Lai and Zhang used alcohols as a solvent for the dehydration reaction system$^{104}$. A significant benefit in using alcohol is the further reaction with HMF to form HMF ethers,
a more stable product that does not undergo polymerization or rehydration. C\textsubscript{1} to C\textsubscript{4} alcohols were used with i-propanol giving the highest yield of HMF, 87%. Reactions were carried at 120°C for 2 h with 5 mol\% HCl as the catalyst. Recycling experiments were also performed by reusing evaporated and recondensed solvent. HMF yields were similar across 5 separate runs, provided the 2 mol\% of HCl was added before each run.

Simeonov et al. used readily crystallizable salts as a solvent to ease separation of HMF after production\textsuperscript{105}. Tetraethylammonium bromide (TEAB) with an Amberlyst-15 catalyst produced yields of >92\% with nearly 100\% HMF selectivity. Reactions were carried out at 100-110°C for 15-90 min. Binder and Raines used various catalysts and additives in a 10 wt\% fructose in DMA system\textsuperscript{106}. The highest yields (> 89\%) came with 6 mol\% H\textsubscript{2}SO\textsubscript{4} and 10 wt\% of alkali metal bromide or iodide salts. The reaction temperature was 100°C and the reaction time was 2-6 hours.

Tong and Li used a small amount of ionic liquid (7.5 mol\%) in DMSO as a catalyst\textsuperscript{107}. Using the ionic liquid N-methyl-2-pyrrolidonium methyl sulfonate [NMP]CH\textsubscript{3}SO\textsubscript{4} at 90°C a 72.3\% yield of HMF at 87.2\% selectivity was achieved after 2 hours of reaction. Sidhpuria et al. immobilized an ionic liquid, 1-(tri-ethoxy silyl-propyl)-3-methyl-imidazolium hydrogen sulfate, onto silica nanoparticles of 300 or 600 nm size\textsuperscript{108}. The highest HMF yield attained was 63\% at full conversion. The reaction was performed in pure DMSO at 130°C for 30 minutes.

Caes and Raines used sulfolane as a solvent with various metal chloride salts as catalysts\textsuperscript{109}. LiCl provided the highest yield at 67\% with the separate selectivity or conversion not reported. Reactions were performed at 90°C for 2 hours with equal
weights of fructose and catalyst. Tong et al. used an iron salt catalyst, FeCl\(_3\), with a co-catalyst\(^{110}\). At 90°C after 2 hours in N-methylpyrrolidone, the highest yields achieved were 82-86% at full conversion. The most active co-catalysts were tetraethylammonium bromide (Et\(_4\)NBr), NH\(_4\)Br, and Et\(_4\)NCl.

Using a flow reactor, Antal et al. added 2 mM H\(_2\)SO\(_4\) as a catalyst to 0.05 M fructose in water and attained about ~50% HMF yield at ~93% conversion under optimal conditions\(^{64}\). Reactions were carried out at 250°C and 34.5 MPa. Another system for the continuous production of HMF from fructose used an Amberlyst-15 resin catalyst with DMSO as a solvent\(^{111}\). Under optimal condition, a 92% HMF yield at 98% conversion was attained. At 110°C, the catalyst system was relatively stable up to 96 hours. In the system used, the yield was maximized by decreasing the Amberlyst particle size to 0.2 mm, increasing the flow rate to minimize external mass transfer limitations, and increasing temperature to increase reaction rate.

Another reaction system used a sulfonic acid-functionalized mesoporous silica catalyst with a single phase mixture of 4:1 (w/w) THF:water\(^{112}\). While the silica has better ex situ thermal stability than an Amberlyst-15 resin (170°C reaction temperature vs. 120°C max operating temperature for the resin), it was less stable under reaction conditions. During reaction, the catalyst was gradually deactivated as fructose conversion decreased from ~90% at 10 hours on stream to ~40% after 60 hours. The selectivity to HMF ranged from 60-70%. Tucker et al. also experimented with a carbohydrate derived compound, DHMTHF, as a cosolvent with water to give up to ~70% HMF selectivity at ~85% conversion\(^{113}\). The reaction was carried out at 130°C, in 1:9
water:DHMTHF with Amberlyst-70 as the catalyst. Decreasing the amount of DHMTHF led to decreases in the initial reaction rate and HMF yield.

Huang et al. impregnated Nafion onto mesocellular silica foams (MCF) to use as an acid catalyst\textsuperscript{114}. In DMSO at 90°C for 2 hours, up to an 89.3% yield was achieved at 95.0% selectivity. The yield was decreased if a different organic solvent was used. Overall, HMF yields for the organic solvents were generally low except for those obtained from high boiling point organic solvents such as DMSO, which would ultimately cost a significant amount of energy to separate HMF via distillation. Accordingly, HMF synthesis from fructose in a biphasic system has been explored to alleviate such hurdles as discussed below.

1.4.2 Fructose Dehydration in Biphasic Systems

Rigal et al. used a system consisting of water and methylisobutylketone (MIBK) in a 1:9 (v/v) water-organic ratio with an ion-exchange resin as an acid catalyst\textsuperscript{115}. A range of different gel-type and macroreticular strong acid resins were used with varied $\text{H}^+$ capacity, surface area, porosity, pore volume, and operating temperature. For reaction at 88°C and 4 h, HMF yield was $\sim$10-35% at selectivities of 30-60%. After 15 h of reaction, the highest yield of HMF was obtained, 56% at 66% selectivity. In another study, Rigal et al. investigated the effect of reaction time, temperature, water-MIBK ratio, catalyst concentration, fructose concentration, stir rate, and resin particle size distribution\textsuperscript{116}. In short, longer reaction times, higher temperatures, or higher fructose concentrations had a beneficial effect on HMF yield, but also led to higher LA yields. Increasing the amount
of MIBK used relative to the amount of water had a positive effect on HMF selectivity, but a lower yield was achieved. Increasing the amount of catalyst also increased HMF yield, but had less of a negative effect on HMF selectivity. Increasing the stir rate had a positive effect on HMF yield and a limited effect on LA formation. Using smaller particles had a positive effect on LA yield.

Rivalier et al. evaluated a range of zeolites for their use in a continuous solid-liquid-liquid extraction reaction. Zeolite and fructose were added to a 1:5 (v/v) mixture of water:MIBK. The reactors were pressurized with N₂ to 10 bar and heated to 165°C. After a 60 minute reaction time with no catalyst, HMF selectivity was 38% at 32% conversion. A zeolite catalyst, H-ZSM5, gave 59% HMF selectivity at 90% conversion. HY-faujasite and H-mordenite were each tested at four different Si/Al ratios. The highest yield from HY-faujasite was with a Si/Al = 10 or 15, where HMF yield was ~40% at ~75% conversion. The highest yield from H-mordenite was with a Si/Al = 11 where selectivity was 91% at 76% conversion. In a subsequent article, H-mordenite was tested at six different Si/Al ratios. However, the new H-mordenite catalysts tested all gave lower yields of HMF when compared to the H-mordenite with a Si/Al = 11.

Román-Leshkov et al. used phase modifiers to promote the partitioning of HMF to the organic phase after formation. Specifically, polar aprotic solvents (DMSO or 1-methyl-2-pyrrolidinone (NMP)) and a hydrophilic polymer (poly(1-vinyl-2-pyrrolidinone (PVP)) were added to the aqueous phase, while 2-butanol was added to MIBK in the organic phase. Using three modifiers, DMSO, PVP, and 2-butanol, with an initial fructose loading of 30 wt% in the aqueous phase, a reaction temperature of 180°C, and a
reaction time of 2.5-3 minutes, an 83% HMF selectivity was achieved at 82% conversion. Scheme 10 shows the biphasic reaction design. The Dumesic group saturated the aqueous phase with NaCl to help promote the partitioning of HMF to the organic phase and thereby improved selectivity and yield\textsuperscript{119}. The authors also tested different organic solvents for the extracting phase; primary and secondary alcohols, ketones, and cyclic ethers. Generally, C\textsubscript{4} solvents gave the highest yields of HMF as compared with the C\textsubscript{3}, C\textsubscript{5}, and C\textsubscript{6} compounds.

Chheda et al. was able to obtain high selectivities from fructose, 87-90\% at nearly full conversion\textsuperscript{120} using an aqueous phase of 1:1 (w/w) water:DMSO and an organic phase of 7:3 (w/w) MIBK:2-butanol. HCl was used as the catalyst and reactions were performed at 170\(^\circ\text{C}\) for 4-8 minutes with a 10 wt\% initial fructose loading. In a separate publication, up to 85\% selectivity at 98\% conversion was attained from fructose\textsuperscript{121}. For this case, the aqueous phase was 4:6 (w/w) water:NMP, MIBK the organic phase, 90\(^\circ\text{C}\) reaction temperature, resin catalyst, and an 18 hour reaction time. DMSO-water mixtures were also used and gave similar yields of HMF.

Chan et al. evaluated 12 different metal chloride catalysts using a biphasic system\textsuperscript{122}. In the system, the ionic liquid, [BMIM]Cl, was used as the polar phase, and THF was used as the organic phase. At low temperature (50\(^\circ\text{C}\)), WCl\textsubscript{4} and WCl\textsubscript{6} were the most promising catalysts giving HMF yields of ~60\% after 4 hours although the separate fructose conversion or HMF selectivity were not given.

Bifunctional solid catalysts, consisting of thioether groups and sulfonic acid groups integrated into ordered mesoporous silica, achieved a 74\% HMF selectivity at 66\%
fructose conversion\textsuperscript{123}. Reaction occurred at 180°C for 30 min with a 30 wt% fructose loading and a 7:3 (w/w) MIBK/2-butanol organic phase. By comparison, when the sulfur groups were grafted onto non-porous silica, HMF selectivity was 61% and conversion 62%, while reaction time was four times longer, 120 min. Further research with acid-functionalized mesoporous silica showed similar yields of HMF\textsuperscript{124}. At 130°C, a 30 wt% fructose loading in water with a 7:3 MIBK:2-butanol organic layer after 141 min gave a HMF yield of 60% at 84% conversion.

A solid acid, Nb\textsubscript{2}O\textsubscript{5}, was used by Yang et al. to attain up to an 89% yield of HMF at 92% conversion\textsuperscript{125}. The highest yield was produced in a biphasic reactor with 20 mL of water and 30 mL of 2-butanol at 160°C for 50 min. Yields decreased when the temperature was lowered or if the catalyst or fructose concentrations were decreased. Another Lewis acid, boric acid, B(OH\textsubscript{3}), was used to get a yield of \~28% at \~52% conversion\textsuperscript{126}. With added NaCl, the yield increased to \~45% at a conversion of 70%. The temperature was 150°C for 45 minutes in 1:4 water:MIBK starting with 30 wt% fructose, 100 g/L B(OH\textsubscript{3}), and 50 g/L NaCl.

Ordomsky et al. used zeolites in a water:MIBK system for fructose dehydration\textsuperscript{127}. The addition of MIBK led to an increase in HMF selectivity when compared with a purely aqueous system, \~80-90% to \~30-40%, respectively. Selectivity was improved upon silylation and deactivation of the external surface acid sites.

Fan et al. used a heteropolyacid, Ag\textsubscript{3}PW\textsubscript{12}O\textsubscript{40}, to obtain yields of \~70-78% at \~75-100% conversion, with the highest yield being 77.7% at 82.8% conversion\textsuperscript{128}. Reactions were carried out in a water/MIBK biphasic system at 120°C for 60-120 min. The highest
yields occurred at shorter reaction times and higher amounts of MIBK. Ag₃PW₁₂O₄₀ also gave the highest yield among the different catalysts tested in the study, which included AgNO₃, H₃PW₁₂O₄₀, Cs₃PW₁₂O₄₀, and HCl. The effect of initial feedstock concentration and temperature were also probed. Similar results as other literature studies were obtained. Namely, lower fructose loadings and higher temperatures led to higher HMF yields. Zhao et al. used another heteropolyacid, Cs₂.₅H₀.₅PW₁₂O₄₀, and obtained up to a 74% yield at 78% conversion. The reactions were performed at 115°C for 60 minutes in 1:3 water:MIBK with 30 wt% fructose initial loading. Zhao et al. also studied the effect of reaction time, ratio of aqueous and organic solvents, and catalyst loading. Generally, higher yields came at longer reaction times, greater amounts of MIBK, and higher catalyst loadings.

Okano et al. used a biphasic system of water and acetonitrile and the introduction of an ionic liquid catalyst, 1-methyl-3-(butyl-4-chlorosulfonyl)imidazolium chlorosulfate, [MBCIm]SO₃Cl. The ionic liquid and HMF partitioned to the organic, however, the ionic liquid was removed to a pseudo-ternary phase by treatment with alumina leaving HMF in the organic phase. Up to 88.7% yield of HMF was achieved at 80°C after 4 h in this system.

Brasholz et al. used a continuous HMF production system and obtained up to an 81% yield. The aqueous phase contained 0.56 M fructose and 32% HCl. The organic phase was dichloromethane. Reactions were carried out at 100°C with a residence time of 1.67 minutes. In a different flow reactor setup, McNeff et al. was able to get 18% yield of
HMF. The reaction was performed at 200°C with a 3 minute residence time, TiO$_2$ catalyst, 3:1 aqueous:$n$-butanol ratio, and a 23 wt% fructose loading.

1.4.3 Fructose Dehydration in Ionic Liquid

Lansalot-Matras and Moreau explored a hydrophilic [BMIM]BF$_4$ or hydrophobic [BMIM]PF$_6$ ionic liquid with DMSO as the cosolvent and Amberlyst resin as the acid catalyst. Under reaction at 80°C, with fructose in pure DMSO only trace of amounts of HMF was formed. With the ionic liquid present at 5:3 [BMIM]BF$_4$:DMSO, the yield of HMF was 27% after 15 hours and 36% after 32 hours. Upon addition of Amberlyst-15, the yield of HMF increased to ~75% after 32 hours, and when the catalyst amount was doubled, the yield increased further to ~87%. For the hydrophobic ionic liquid, [BMIM]BF$_4$, HMF yield was ~70% after 24 hours and when the Amberlyst amount was doubled the subsequent HMF yield obtained was ~80%.

Zhao et al. used [BMIM]Cl to achieve ~72% yield at 100% conversion at 120°C and 3 hours. At 100°C, the yield was ~40% at ~58% conversion, and at 80°C, the yield was ~1% at ~5% conversion. Yong et al. were able to achieve up to a 96% yield of HMF from fructose using N-heterocyclic carbene (NHC)-chromium (Cr$^{II}$ and Cr$^{III}$) complexes in [BMIM]Cl. Reaction conditions were: 100°C, 6 hours, 10 wt% fructose loading, and 9 mol% catalyst loading. High yields of HMF were achieved with a GeCl$_4$ catalyst in [BMIM]Cl. At 100°C after 5 min, HMF yield was 92.1% at full conversion. GeCl$_4$ gave the highest yields as compared to 6 other metal chlorides that were tested. As a result, GeCl$_4$ was subsequently examined in the dehydration of other carbohydrates.
Xie et al. used sulfonated lignin as an acid catalyst in [BMIM]Cl\textsuperscript{136}. At 100°C, the maximum HMF yield was achieved after 10 minutes with a value of ~94% at ~98% conversion. The ionic liquid (~83% yield at 100% conversion) afforded higher yields of HMF when compared to the polar aprotic solvents DMSO (~80% yield at 100% conversion), NMP (~55% yield at ~95% conversion), and dimethylacetamide (DMA, ~35% yield at ~75% conversion) at 100°C for 40 minutes. Qi et al. sulfonated a cellulose-derived carbonaceous solid and attained an 83% yield when the reaction was performed at 80°C for 10 minutes in [BMIM]Cl with a 1 wt% fructose loading and 5 wt% catalyst loading\textsuperscript{137}. Lima et al. obtained up to 88% yield at full conversion in [BMIM]HSO\textsubscript{4}\textsuperscript{138}. The reaction was performed at 100°C for 30 minutes with MIBK as an extracting solvent.

Hu et al. experimented with a wide range of ionic liquids\textsuperscript{139}. The highest yields were obtained in choline chloride with citric acid as a catalyst, particularly when ethyl acetate was used to extract HMF. At 80°C and 1 hour, the yield in choline chloride was ~75% at ~91% conversion. With intermittent extraction, the yield increased to ~86% at ~94% conversion, and with continuous extraction, the yield increased further to ~92% at ~97% conversion.

Using an Amberlyst-15 resin, Qi et al. achieved an 83.3% HMF yield and 98.6% fructose conversion in [BMIM]Cl at 80°C after 10 min\textsuperscript{140}. When the temperature was increased to 120°C, the reaction time decreased to 1 min with a similar yield and conversion. At 80°C, the catalyst and ionic liquid solvent were able to be recycled for seven successive runs without any appreciable loss in activity. In a different study, Qi et
al. added a co-solvent (acetone, DMSO, methanol, ethanol, or ethyl acetate) to the [BMIM]Cl and catalytic resin system\textsuperscript{141}. At 25°C, after 6 hours the HMF yield was ~78% at ~90% conversion.

Zhang et al. encapsulated a heteropolyacid, phosphotungstic acid (PTA), in a chromium-based metal-organic framework (MIL-101)\textsuperscript{142}. Under reaction at 80°C for 60 minutes with 1-ethyl-3-methylimidazolium chloride as a solvent, up to a 63% yield was attained at 84% conversion. When PTA was used without the metal-organic framework, the yield was 80% at 87% conversion.

Kraus and Guney prepared 5-methoxy or 5-ethoxymethylfurfural from fructose in sulfonic acid-functionalized ionic liquids\textsuperscript{48}. The highest yield obtained with methanol as the reagent was 70% (46% for HMF and 24% for MMF), and with ethanol was 64% (21% for HMF and 43% for EMF). The reaction was performed in a biphasic reactor with the ionic liquid and alcohol as the reaction phase and hexane as the extracting phase. The temperature used was 100°C with the highest product yields being obtained at shorter reaction times.

Highly concentrated solutions of fructose in choline chloride were able to give a HMF yield of 70% using initial fructose to choline chloride weight ratios of up to 4:1\textsuperscript{143}. At a 2.5:1 weight ratio the optimal HMF yield was 50%. Reactions were performed at 120°C under 40 bar CO\textsubscript{2} for 90 minutes. In a 2:3 (w/w) solution of fructose:choline chloride and 10 mol\% of p-toluenesulfonic acid, a 67% yield of HMF was obtained after reaction at 100°C for 30 minutes\textsuperscript{144}. Under the same reaction conditions, a 60% yield was achieved with CrCl\textsubscript{3} as the catalyst and was 59% yield with FeCl\textsubscript{3}. 
Vigier et al. used betaine hydrochloride (BHC)\textsuperscript{145}. In a 1:1 (w/w) BHC:glycerol system at 110°C and 10 wt% fructose loading, a 57% yield was obtained. The same yield was attained in 4:1 (w/w) BHC:water with MIBK as an extracting solvent at 100°C after 120 minutes and starting with 20 wt% fructose.

1.5. Glucose Dehydration

Compared to fructose, glucose is the preferred feedstock for HMF production due to its greater availability and lower cost. Therefore, a more recent shift in focus has occurred from fructose to glucose as the starting reactant. In this section, representative glucose dehydration literature articles will be reviewed in monophasic, biphasic and ionic liquid solvent systems. Results for the glucose dehydration reaction from these articles are summarized in Tables 4-6.

1.5.1. Glucose Dehydration in Monophasic Systems

Early research on converting glucose to HMF was primarily focused on monophasic systems with either water or an organic as the reaction media. Glucose decomposition in pure water is non-selective and HMF yields are typically very low. Using a sugar-solubilizing polar organic aprotic solvent such as DMSO can improve HMF yields significantly, possibly due to fewer side-reactions that occur under non-aqueous conditions. However, sugar solubility in most organic solvents is low and, as such, a miscible water-organic binary solvent has been used to perform sugar dehydration reactions.
In 1962, Mednick tested a variety of acids, ammonium salts and combinations of an acid and a base (pyridine) for glucose conversion in pure water (160-190°C) or 1:1 water:dioxane (200-250°C)\textsuperscript{146}. In pure water, HMF was produced by various catalysts with yields ranging from 3 mol% to 23 mol%, with the highest yield of 23 mol% being obtained in the presence of both H\textsubscript{3}PO\textsubscript{4} and (NH\textsubscript{4})\textsubscript{2}HPO\textsubscript{4}. Increased yields of HMF were observed when using combinations of acid and base catalysts in the water:dioxane system at temperatures above 200°C. For example, a 46 mol% HMF yield was achieved with temperatures of 200-228°C, catalyzed by H\textsubscript{3}PO\textsubscript{4}/pyridine.

Seri et al. reported lanthanide(III) cations were very active catalysts to dehydrate glucose in water at 140°C to produce HMF without generating much levulinic acid\textsuperscript{147, 148}. However, low yields of HMF were obtained (<10 mol%) due to the formation of significant amounts of insoluble humins.

Qi et al. used microwave heating to perform glucose dehydration with metal oxides, TiO\textsubscript{2} and ZrO\textsubscript{2}\textsuperscript{149}. Microwave heating was found to promote the formation of HMF. When TiO\textsubscript{2} was used as the catalyst, a 19mol% HMF yield was realized in water at 200°C after 5 min of microwave heating at ~90% glucose conversion. 10 mol% was observed with ZrO\textsubscript{2} under the same reaction conditions. In 2011, Dutta et al. synthesized mesoporous TiO\textsubscript{2} in order to increase surface area and tested the TiO\textsubscript{2} nanoparticles for carbohydrate dehydration\textsuperscript{100}. Glucose was readily converted by microwave heating with this catalyst, at 120°C for 5min and a 25 mol% HMF yield was achieved.
Hara and co-workers have explored two solid acid systems as heterogeneous catalysts for glucose dehydration in aqueous media\cite{150, 151}. In one study, protonated titanate nanotubes with high surface area (~400 m$^2$/g) were used in a system of 1 wt% glucose in aqueous media with an equal weight of catalyst, and a reaction temperature of 120 °C with reaction time of 3 h. A HMF yield of 14 mol% was achieved with titanate nanotubes, whereas only 2 mol% was observed with conventional TiO$_2$\cite{151}. Another report from the same group examined niobic acid, Nb$_2$O$_5$·nH$_2$O, as a heterogeneous water-tolerant Lewis acid\cite{150}. Using Raman and FT-IR spectra, they found that even NbO$_4$ tetrahedra, on the surface of Nb$_2$O$_5$·nH$_2$O, formed NbO$_4$–H$_2$O immediately upon contact with water. The NbO$_4$–H$_2$O adducts could still be coordinatively unsaturated and function as effective Lewis acids. A HMF yield of 12 mol% was obtained using this catalyst with reaction temperature of 120°C and reaction time of 3 h. When Nb$_2$O$_5$·nH$_2$O was used together with H$_3$PO$_4$, an improved HMF yield of 48 mol% was found.

Work in aprotic polar organic solvents primarily focused on DMSO and DMF. Yan et al. prepared super acids SO$_4^{2-/}$/ZrO$_2$ (CZS) and SO$_4^{2-/}$ZrO$_2$-Al$_2$O$_3$ (CSZA) and tested their catalytic activities for glucose conversion in DMSO\cite{152}. Using 130°C and a reaction time of 4h, glucose was completely converted with both the CZS and CSZA catalysts, giving yields between 19 mol% and 48 mol%, compared to 4 mol% in the absence of a catalyst. Takagaki et al. performed glucose dehydration in DMF catalyzed by a combination of solid acid and base catalysts\cite{153}. A HMF yield of 42 mol% was obtained from glucose at a conversion of 73% after 3 h of reaction time at 100°C.
Apart from these conventional aqueous and aprotic polar solvents, the use of alcohols (mainly methanol and ethanol) and carboxylic acids (mainly acetic acid) were also studied. While lower HMF yields from glucose were typically obtained with these solvents relative to DMSO/DMF, it could still be advantageous to employ these solvents, taking into account the easier isolation/purification of HMF from the reaction mixture, and the fact that alcohols and carboxylic acids can react with HMF under reaction conditions to form ethers and esters, respectively, thereby stabilizing the dehydration product. Yang et al. conducted glucose conversion in a 9:1 (w/w) ethanol-water mixed solvent system, using AlCl$_3$ as the catalyst. 1 mmol glucose, 0.4 mmol catalyst, and 4 g of mixed solvent were reacted at 160°C for 15 min$^{154}$. A 24 mol% HMF yield was obtained together with its ether, 5-ethoxymethylfurfural at 33 mol%, resulting in a 57 mol% overall furan yield. Similar protection approaches have been employed with other solvents$^{102,155}$.

1.5.2 Glucose Dehydration in Biphasic System

Before the report by Dumesic and co-workers$^{156}$ on the fructose dehydration using MIBK-water biphasic configuration that revitalized the interest in developing novel biphasic systems for HMF production, the majority of literature on this topic has focused on using fructose as the reactant$^{115,157}$. In this section, updated literature concerning the application of biphasic systems for glucose conversion will be discussed.

In an effort to develop non-corrosive and non-toxic catalysts (compared to conventional homogeneous mineral acids, e.g., H$_2$SO$_4$ and HCl) for glucose conversion to HMF, Hansen et al. used a combination of various salts and boric acid, H$_3$BO$_3$, to
catalyze glucose dehydration in water with MIBK as the extracting organic solvent\textsuperscript{126}. In the study, boric acid functioned as a Lewis acid, which can chelate with diols, resulting in a transient release of a proton to the solution that could act as a Brønsted acid to catalyze dehydration. After all the glucose molecules were consumed, the solution pH returned to the value determined by the boric acid/water equilibrium in solution. A 14 mol\% HMF yield was reported at a glucose conversion of 41\% with a reaction temperature of 150°C and time of 300 min. Other extracting solvents (2-butanol and THF) were also studied and similar conversion and selectivity results were found.

Yang et al. examined the use of H\textsubscript{3}PO\textsubscript{4} treated niobic acid (Nb\textsubscript{2}O\textsubscript{5}·nH\textsubscript{2}O, NA-p) as catalysts for glucose conversion\textsuperscript{125}. 1.2 g glucose was dissolved in 20 mL water with 0.1 g NA-p, and the solution was contacted with 30 mL of 2-butanol. A HMF yield of 49 mol\% was obtained with ~70\% glucose conversion after 110 min reaction time at 170°C. However, HMF yields dropped after 110 min with higher glucose conversion due to the formation of undesired products. Catalyst recyclability studies were performed by comparing sugar conversions and HMF selectivities under identical reaction conditions. The results showed that the catalyst could be reused at least 7 times without significant loss of catalytic performance. The same group also reported tantalum compounds (Ta\textsubscript{2}O\textsubscript{5}·nH\textsubscript{2}O, TA-p) showed strong acidity and could catalyze carbohydrates conversion to HMF as well\textsuperscript{158}. A higher HMF selectivity compared with Nb\textsubscript{2}O\textsubscript{5}·nH\textsubscript{2}O was observed as a reaction time of 140 min and reaction temperature of 160°C led to 70\% of the glucose being converted to give a HMF yield of 58 mol\%. Recently, Xiong et al. prepared niobic acid/carbon hybrid materials\textsuperscript{159}. By tuning the hydrophobicity and
hydrophilicity of the catalyst, the partitioning of the catalyst could be altered between the hydrophilic aqueous phase, hydrophobic organic phase, or the interface. With the catalyst residing in the aqueous phase, a HMF yield of 20 mol% with glucose conversion of 78% at 170°C for 2h was obtained.

Fan et al. reported glucose conversion to HMF in a water-MIBK biphasic system using solid heteropolyacid salt (Ag$_3$PW$_{12}$O$_{40}$) as the catalyst$^{128}$. They proposed that the presence of both Lewis and Brønsted acidity could lead to improved catalytic activity and HMF selectivity. The optimized HMF yield was 76 mol% for a glucose conversion of ~90% at 130°C and 4h with a water to MIBK ratio of 1:2.25. Work from the same group involved using a Brønsted acid-Lewis acid-surfactant combined heteropolyacid catalyst for HMF production directly from cellulose$^{160}$. Cr[(DS)H$_2$PW$_{12}$O$_{40}$]$_3$ (DS is dodecyl sulfate) was synthesized as the composite catalyst. The combined Lewis and Bronsted acidity could catalyze cellulose hydrolysis to glucose with subsequent dehydration to HMF and the hydrophobic core formed by dodecyl group was speculated to provide a microenvironment that protected the produced HMF. Using this strategy, cellulose was quantitatively converted after 4h at 170°C, yielding HMF >70 mol%.

As discussed above, effective operation of these biphasic systems requires high interfacial surface area for effective mass transfer. In this regard, Ordomsky et al. prepared solid acid zirconium phosphate (ZrPO) on an Al foam to address this issue$^{161}$. Silylation was also conducted to reduce the amount of Lewis acidity on the surface of the ZrPO, while increasing the density of Brønsted acid sites with the resultant material
denoted ZrPO/Si. Fewer Lewis sites on the ZrPO/Si led to a decrease in activity but an increase in HMF selectivity, which was due to suppression of humin formation by Lewis acid sites.

1.5.3 Glucose Dehydration in Ionic Liquids

Since the breakthrough work by Zhang et al.\textsuperscript{76} in utilizing ionic liquids (IL) as solvents and co-catalysts for HMF production from carbohydrates (fructose and glucose), an expanding interest has been reflected in the rapidly growing number of reports in the literature in using ILs. Several excellent reviews have summarized this topic\textsuperscript{35, 60}. In this section, we will summarize the work on different compositions of ILs, catalysts and reaction conditions and how these factors affected glucose conversion activity and the ultimate HMF yields.

Binder et al. reported a simple reaction system for the conversion of glucose, fructose and full lignocellulosic biomass using a solvent system that resembled the properties of ILs\textsuperscript{106}. In their strategy, the polar aprotic organic solvent DMA was modified with LiCl, which was used to successfully solubilize carbohydrates. By optimizing the composition of CrX\textsubscript{n} (X=Cl, Br; n=2,3) and [BMIM]Cl, the highest glucose molar yield of 80% was achieved with a catalyst system composed of DMA-LiBr(10%), 6 mol% CrBr\textsubscript{3} catalyst, and reaction conditions of 6 h at 100°C.

Later, a Brønsted acid (H\textsubscript{2}SO\textsubscript{4}) was added to the ionic liquid [BMIm]Cl by Sievers et al. to test the effectiveness in converting glucose, fructose and mannose to HMF\textsuperscript{162}. Interestingly, a low HMF yield of only 12 mol% was obtained from glucose, which was significantly lower than the results by Zhang et al.\textsuperscript{76}. This result suggested that for
efficient glucose transformation to HMF under this condition a Lewis acid (e.g., CrCl₂) is advantageous.

Microwave irradiation (MI) was found to play a key role in controlling HMF selectivities when using ILs. Li et al. observed that a HMF yield of 91 mol% could be achieved in [C₄mim]Cl with a CrCl₃ catalyst using MI at 100°C for 1 min. A conventional oil-bath heating method was used for comparison. For similar conversion values (60 min of reaction in the conventional system) only a 17 mol% yield was obtained. Qi et al. reported similar observations on the enhancement effect of using MI as the heating method. In their study, a 71 mol% HMF yield was achieved in a reaction system with [BMIM]Cl and a CrCl₃ catalyst.

Instead of using the effective CrClₓ (x = 2, 3) catalyst employed by in the above work, Hu et al. extended the catalysts to include a commonly used Lewis acid, SnCl₄. They ran the reaction at 100°C for 3 h in [BMIM]BF₄, obtaining a HMF yield of 61 mol%. Zhang et al. later examined the use of GeCl₄ to replace the toxic chromium and tin as a Lewis acid for glucose dehydration. The reaction conditions were 5 wt% glucose dissolved in [BMIM]Cl, followed by heating at 120°C for 30 min. A moderate HMF yield of 48 mol% was detected. To that end, Khokhlova et al. also reported B₂O₃ as an environmentally benign metal-free promoter for carbohydrate conversion in ILs.

A study by Liu et al. demonstrated that ubiquitous aluminum alkyl or alkoxy compounds were effective Lewis acids for glucose to HMF transformation in ILs. At 120°C for 6 h, HMF yields from glucose catalyzed by Al(O'Sr)₃ and AlEt₃ were 49 mol% and 51 mol %, respectively. Chen and co-workers also reported Cr⁰ nanoparticles could
function as effective catalysts for the glucose to HMF conversion\textsuperscript{168}. A moderate yield of 49 mol\% in [BMIM]Cl was obtained from 23 wt\% glucose solution using reaction conditions of 120°C for 6 h.

To address the challenge of catalyst recycling and separation from the reaction system, Zhang et al. prepared hydroxyapatite-supported chromium chloride (Cr-HAP) and examined its activity\textsuperscript{169}. With MI heating at 150°C for 2.5 min, they reported a HMF yield of 40 mol\% at a glucose conversion of 78\%.

1.6. Combined Glucose to Fructose Isomerization and Fructose Dehydration to HMF Strategy

After reviewing the current approaches used to convert glucose to HMF, it is apparent that an aqueous-organic biphasic system is generally attractive for improving HMF yields. MCl\textsubscript{x}/ionic liquids were also used to convert both glucose and fructose to HMF in high yields. However, the commercial use of expensive ILs as a processing solvent is challenging due to the stability and purity requirements for the ILs\textsuperscript{170}. Progress has been made in combining a glucose isomerization catalyst with a fructose dehydration catalyst in either a “one-pot” or “two-step” configuration. Based on the knowledge that Brønsted acid catalysts give the best HMF selectivities for the fructose dehydration step, researchers have pursued the identification of effective glucose isomerization catalysts and successes have been reported in using bases, enzymes, or Lewis acids for this purpose. As such, isomerization of glucose can therefore be integrated with fructose dehydration to produce HMF (Scheme 11).
1.6.1. Combined Base and Brønsted Acid Systems

In general, glucose/fructose isomerization is known through the Lobry-deBruyn-van Ekenstein transformation, which is catalyzed by a base. Takagaki et al. hypothesized a tandem approach, which consisted of a solid base catalyst for isomerization of glucose to fructose and a solid acid catalyst for fructose dehydration\textsuperscript{171}. After initial catalyst screening for the activity of the two individual steps, Mg-Al hydrotalcite and Amberlyst-15 were chosen as the solid base and acid, respectively. To create site isolation of acids and bases, an organic aprotic solvent was the preferred solvent since it can minimize the possibility of mutual interaction of an acid/base pair. DMF was selected as the media for this “one-pot” transformation. The combination of the base and acid catalysts was demonstrated to be effective, achieving glucose conversion of 73% with selectivity towards HMF of 58%.

Despax et al. later examined the effectiveness of sodium aluminate (NaAlO\textsubscript{2}) and HCl as a solid base and acid pair for glucose conversion and achieved up to 82 mol% HMF yield\textsuperscript{172}. DMSO was used as the solvent, which may cause concerns about the ultimate separation and purification of HMF.

1.6.2. Combined Enzymatic and Brønsted Acid Catalysts Systems

Enzymes are a potentially attractive catalysts for performing glucose isomerization to fructose because of their high selectivity under mild reaction conditions\textsuperscript{173}. A multi-step novel reactor design and separation scheme was shown that allowed for very high yields of HMF directly from glucose (up to ~90 mol%). However, concerns still remain
in the application of enzymes due to the need to perform multiple and separate processing steps.

Huang et al. used a combination of glucose isomerase and sodium tetraborate to transform glucose to fructose\(^{174}\). A fructose yield of up to 88 mol% (equilibrium without borate is ~50% maximum yield) was realized by exploiting the superior chelating effect of sodium tetraborate with ketoses (fructose) relative to aldoses (glucose). After the separation of fructose from the glucose isomerase, a second, HCl-catalyzed step for fructose dehydration was conducted in a biphasic configuration with 1-butanol as the organic extracting solvent. The overall glucose conversion from glucose was 88% with the final HMF yield reaching 63 mol%.

Grande et al. reported a chemo-enzymatic process that could be performed in seawater as an abundantly available and environmentally friendly solvent\(^{173}\). In their experiments, they used immobilized D-glucose/xylose isomerase (EC 5.3.1.5) for the isomerization of glucose to fructose until the equilibrium yield of fructose was reached (ca. 50:50 glucose/fructose). Then in a separate second-step, fructose (without glucose present) was dehydrated by oxalic acid in a biphasic system with 2-methyltetrahydrofuran (2-MTHF) as the extracting solvent to give 57 mol% yields in seawater. Although the individual isomerization/dehydration steps could be performed in seawater, an integrated process, which directly uses the fructose/glucose mixture produced in the isomerization step, would be required for practical application.

The ionic liquid N,N-dibutylethanolammonium octanoate (DBAO) was also used by Riisager and co-workers as the media for enzymatic glucose isomerization\(^{175}\). In their
study, Sweetzyme® was chosen as a model glucose isomerase and different ILs were screened as a solvent for glucose to fructose isomerization. Kinetic analysis of glucose isomerization catalyzed by Sweetzyme® in DBAO was performed and it was revealed that a longer reaction time (4h) was required to reach the glucose/fructose equilibrium compared to an experiment done in an aqueous media (0.5h).

An interesting report by Li et al. outlined a novel simultaneous glucose isomerization and reactive-extraction strategy to separate the in-situ produced fructose (Scheme 12)\textsuperscript{176}. In the first glucose isomerization step (12a), enzymes were used to catalyze the transformation to an equilibrium mixture of glucose and fructose. To shift the equilibrium to favor ketose formation, an effective method could be removal of the ketose. The authors devised a biphasic system in which a hydrophobic aryl boronic acid (ABA) containing organic phase could continuously and selectively extract the ketose into the organic phase, whereas the aldose-form of the sugar was held in the aqueous phase where the isomerization occurred. In a second step (12b), contact with an acidic aqueous layer separated the conjugated ketose-ABA complex. This integrated process resulted in a pure ketose stream from aldose sugars, creating the possibility for integration with a subsequent dehydration reaction step. Recent work from the same research group described the use of this strategy to perform a xylose to xylulose to furfural tandem reaction. Under a relatively mild reaction temperature of 110°C, they reported over an 80 mol% yield of furfural from xylose\textsuperscript{177}.

Simeonov et al. also studied the chemo-enzymatic strategy for efficient glucose to HMF conversion\textsuperscript{105,178}. In their reports, Sweetzyme® was applied as the isomerization
catalyst in a wet tetraethylammonium bromide (TEAB) media (Scheme 13). Conducting isomerization and dehydration in the same media and recycling the unreacted glucose from the second step allowed the highest reported yield of HMF, 91 mol% from glucose.

1.6.3 Combined Lewis Acid and Brønsted Acid Systems

In contrast to the two-step requirement for the combined chemo-enzymatic approach, combined Lewis and Brønsted acid catalyst systems could provide a more easily integrated “one-step” process in an aqueous media\textsuperscript{179}. In general, a Lewis acid is required for glucose isomerization to fructose, followed by a Brønsted acid-catalyzed dehydration of fructose to HMF. The Lewis acids reported in literature have been either heterogeneous zeolitic Lewis acids or homogeneous metal salts.

1.6.3.1. Solid Lewis Acid and Brønsted Acid Systems

In 2010, a tin-containing beta zeolite (Sn-Beta) was reported to be an active catalyst for the isomerization of glucose to fructose in water with activities and selectivities rivaling those of enzymes\textsuperscript{180}. Subsequently, several mechanistic studies have been performed to elucidate how the isomerization reaction proceeds in the presence of Sn-Beta\textsuperscript{74, 75}. It was shown that the hydrophobic Sn-beta provides a microenvironment that appears to be analogous to that in a metalloenzyme, glucose isomerase. NMR, in conjunction with labeling experiments, showed that glucose could enter the micropores of the zeolite and undergo glucose/fructose isomerization via a 1,2-hydride transfer mechanism catalyzed by the tin Lewis acid center. Unlike its enzyme counterparts, Sn-beta can function under acidic conditions and elevated temperatures, which made it possible to integrate the subsequent acid-catalyzed fructose to HMF conversion.
Nikolla et al. exploited the combination of Sn-beta with HCl for glucose conversion in a biphasic system (Scheme 14)\(^8\). A HMF selectivity of 55 mol% was obtained at a glucose conversion of 75% with the combination of Sn-beta and HCl at 160°C for 90 min in a water/1-butanol biphasic system. When only Sn-beta was used, a 18 mol% HMF selectivity at 75% glucose conversion was observed and with only HCl a 40 mol% HMF selectivity at 26% glucose conversion. The improved overall HMF yield from Sn-beta/HCl was attributed to the synergistic catalytic activity for the individual isomerization/dehydration steps. Further optimization of the catalytic system gave a HMF selectivity of 72 mol% at 79% glucose conversion with reaction conditions of: water/THF biphasic system, catalysis by a combination of Sn-beta and HCl, reaction temperature of 180°C, and reaction time of 70 min.

Lew et al. reported application of the combination of Sn-beta and an acidic resin, Amberlyst, for the synthesis of 5-EMF directly from glucose in ethanol\(^4\). A 31 mol% yield of EMF was obtained with the combined Sn-beta/Amenberlyst catalysts at 90°C.

While quite promising, Sn-beta is not a commercially available zeolite, is challenging to prepare and introduces environmental concerns associated with the toxic element, tin. To overcome these concerns, Saravanamurugan et al. used different types of commercially available zeolites and described a two-step pathway to make fructose from glucose in methanol and water\(^1\). In the first step, glucose was isomerized to fructose and then the fructose was reacted with methanol to form methyl fructoside. In the second step, methyl fructoside was hydrolyzed by the addition of water, resulting in fructose production (Scheme 15). Y-zeolites were found to be the most effective catalysts. After
optimization, high fructose yields (>50 mol%) were achieved using this two-step process with H-USY(6). However, the limited solubility of glucose in alcohol could be a concern for this approach since only a 3 wt% glucose in methanol was used, whereas a 45 wt% glucose aqueous solution was used in the abovementioned work by the Davis group.180

In addition to using Sn-Beta for C₆ sugars conversion, a considerable amount of work has also been reported on the dehydration of C₅ sugars to furfural in high yields182.

1.6.3.2. MClₓ-Type Lewis Acid and Brønsted Acid Systems

Another area that has attracted growing interest for glucose to HMF conversion involves the use of a combination of various MClₓ-type Lewis acidic metal salts (M represents the metal) and Brønsted acids, typically HCl. It has been shown that the solution pH plays a key role in controlling the Lewis acidity of the MClₓ catalyst183. In that regard, traditional moisture-sensitive and water-compatible metal salts both have been tested as catalysts for the glucose dehydration reaction under appropriate pH conditions.

In 2012, Dumesic and co-workers reported a catalytic system in which a combination of Lewis acidic metal salts (e.g., AlCl₃, SnCl₄, GaCl₃, YbCl₃, LaCl₃) and HCl were used for glucose conversion in a biphasic system81. Depending on the nature of the MCl₃ the different metal salts had different activity in catalyzing glucose conversion. In order to compare selectivity towards HMF for various catalysts, a similar glucose conversion (~90%) was targeted. At this conversion level, the HMF yields ranged from ~40 mol% to ~60 mol% based on glucose. AlCl₃ gave the highest selectivity of 67 mol%. The authors attributed the different activities of the MCl₃ catalysts to their intrinsic Lewis
character, such as the ionic radius of the cation, hardness/softness of the Lewis acid, metal speciation, etc. Another study by Wang et al. revealed that using water-compatible Lewis acids (e.g., YbCl₃, DyCl₃, LaCl₃), could promote glucose conversion under higher solution pH values (~5)⁸². Other carbohydrates such as cellobiose, starch, or even cellulose could be converted to HMF in moderate yields.

Yang et al. achieved 61 mol% HMF yield from glucose using a similar combined Lewis acid, AlCl₃, and Brønsted acid, HCl, after 10 min of microwave heating at 160°C in a water-THF biphasic system⁸³. The authors attributed the activity of this reaction system to a synergistic effect between AlCl₃ and HCl. Another report from the same group extended this catalyst system to perform xylose dehydration with a similar aldose/ketose isomerization followed by dehydration to give a furfural yield of 75 mol%⁷³.

As CrCl₃ has been widely used in IL-based glucose dehydration systems, Vlachos and co-workers have successfully demonstrated their activity for C₅ sugar dehydration in a water-organic biphasic system⁷²,⁸⁵. In a recent publication, the authors have used experimental kinetic data and computational methods to decipher the interplay between Lewis and Bronsted acidity in controlling the activities and selectivities in C₆ sugar (glucose and fructose) dehydration⁸⁶.

Deng et al. reported the use of concentrated ZnCl₂ as a water-compatible Lewis acid for the conversion of various carbohydrates to HMF¹⁸⁴. The high concentration of ZnCl₂ in water was proposed to facilitate coordination with the hydroxyl/carbonyl groups in glucose thereby catalyzing glucose isomerization to fructose. The protons generated by
the ZnCl₂-acidified solution could then catalyze fructose dehydration. At 120°C, after full conversion of the carbohydrate, 16 mol% and 53 mol% HMF yields were obtained from glucose and fructose, respectively. A combination of ZnSO₄ and NaHSO₄ was explored by Shi et al. to convert cellulose directly to HMF giving a 53 mol% yield\textsuperscript{185}. The reaction was run in a water-THF biphasic system with a reaction temperature of 170°C and time of 60 min.

1.7. Conclusion and Outlook

Interest in HMF production has experienced a rapid expansion over the past decade. Not only have researchers utilized more abundantly available feedstocks, but also novel catalysts, processing solvents, reaction engineering and HMF derivatization have been explored leading to a revitalized interest in HMF. Recent significant breakthroughs in the field include, but are not limited to, the use of ILs as novel solvents and co-catalysts and the combination of CrClₓ/IL as an effective catalyst system to convert C₆ sugars. Also, a novel reaction engineering approach involving the reemergence and modification of water-organic biphasic systems have shown dramatically improved HMF yields. Another important development is the used of either heterogeneous or homogeneous Lewis acid catalysts, which can activate C₆ sugars in aqueous media.

However, important challenges still remain to be solved before a large-scale economical process for HMF production can be realized. For example, a thorough mechanistic investigation of glucose conversion to HMF including understanding of byproduct formation is needed to guide further catalyst design and/or catalytic process integration. Also techno-economic analysis of the HMF production strategies are required.
as well the environmental impact of the upstream and downstream processing to generate HMF from carbohydrate feedstocks. The rapid rate of recent innovation in HMF production suggests that a viable process will be realized.

References:


Schemes and Figures

Scheme 1. Lignocellulose biomass composition: cellulose, hemicellulose, and lignin.

Scheme 2. Thermochemical routes for converting lignocellulosic biomass to renewable fuels and chemicals.

Scheme 3. Chemical structure of HMF.
Scheme 4. Overall reaction scheme and proposed mechanism for the oxidation of HMF in aqueous solution in the presence of excess base (OH-) and either Pt or Au. From reference 57.

**HMF Oxidation Scheme**

Scheme 5. Conversion of HMF to DMF and 5-alkoxymethylfurfural ethers as biofuels
Scheme 6. Triple dehydration of hexose to synthesize HMF.

Scheme 7. Possible hexose dehydration pathways (decomposition via fructose isomerization (O); acyclic route (□); cyclic route (△)). Reprinted from reference 10 with permission.
Scheme 8. Proposed metal chlorides interaction with glucose to produce HMF. From reference 95.

Scheme 9. Proposed mechanism of glucose isomerization to fructose (M=various metal Lewis acid centers). Adapted from reference 93.
Scheme 10. Representation of biphasic reactor design for HMF production. From reference 139.

Scheme 11. Synthesis of HMF from glucose using combined isomerization/dehydration catalysts.
Scheme 12. Process of (a) reactive extraction and (b) sugar recovery via stripping. From reference 200.

Scheme 15. Reaction pathway for fructose formation from glucose in alcohol and aqueous media. From reference 205.

Table 1. Fructose dehydration in monophasic system.

<table>
<thead>
<tr>
<th>Fructose loading (M)</th>
<th>Solvent</th>
<th>catalyst</th>
<th>catalyst loading (M)</th>
<th>T/°C</th>
<th>Time (min)</th>
<th>Conv (%)</th>
<th>Selectivity (%)</th>
<th>Yield (%)</th>
<th>Ref.</th>
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<td>HCl</td>
<td>2 M</td>
<td>95</td>
<td>24</td>
<td>75</td>
<td>41</td>
<td>31</td>
<td>106</td>
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<tr>
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<td>Water</td>
<td>HCl</td>
<td>1 M</td>
<td>95</td>
<td>30</td>
<td>92</td>
<td>76</td>
<td>70</td>
<td>106</td>
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<tr>
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<td>DMSO</td>
<td>Diaion PK-216</td>
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<td>80</td>
<td>40</td>
<td>-</td>
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<td>-</td>
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<td>120</td>
<td>-</td>
<td>-</td>
<td>92</td>
<td>111</td>
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<tr>
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<td>Water</td>
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<td>1 M</td>
<td>88</td>
<td>300</td>
<td>~65</td>
<td>~20</td>
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<tr>
<td></td>
<td>Component 1</td>
<td>Component 2</td>
<td>Concentration</td>
<td>Volume Ratio</td>
<td>Reaction Temperature</td>
<td>Reaction Time</td>
<td>Product Yield</td>
<td>Product Purity</td>
<td>Product Temperature</td>
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</tr>
<tr>
<td>0.5 M 1:1 (v/v)</td>
<td>pTSA</td>
<td>1 M</td>
<td>88</td>
<td>300</td>
<td>&gt;90</td>
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<td></td>
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</tr>
<tr>
<td>0.5 M 1:1 (v/v)</td>
<td>pTSA</td>
<td>1 M</td>
<td>88</td>
<td>300</td>
<td>&gt;90</td>
<td>~45</td>
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<td>250</td>
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<td>93</td>
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<td></td>
<td>wt%</td>
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<td></td>
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<td>VOP</td>
<td>3.6</td>
<td>80</td>
<td>30</td>
<td>46.6</td>
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<td>115</td>
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<td>80</td>
<td>30</td>
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<tr>
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<td>a-TiO2</td>
<td>8.3</td>
<td>200</td>
<td>5</td>
<td>100</td>
<td>~20</td>
<td>~20</td>
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<td>m/c-ZrO2</td>
<td>8.3</td>
<td>200</td>
<td>5</td>
<td>~85</td>
<td>~13</td>
<td>~15</td>
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<tr>
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<td>100</td>
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<td>100</td>
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<td>36.7</td>
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<td>C-ZrP2O7</td>
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<td>100</td>
<td>30</td>
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<td>44.3</td>
<td>119</td>
<td></td>
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<tr>
<td>2 wt% 3:7 (w/w)</td>
<td>Dowex</td>
<td>2</td>
<td>150</td>
<td>15</td>
<td>95.1</td>
<td>77.2</td>
<td>73.4</td>
<td>121</td>
<td></td>
</tr>
<tr>
<td>Water/Acetone</td>
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<tr>
<td>0.5 M i-propanol</td>
<td>HCl</td>
<td>5</td>
<td>120</td>
<td>120</td>
<td>-</td>
<td>-</td>
<td>83</td>
<td>124</td>
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<tr>
<td>20 wt% Water/TEA</td>
<td>Amberlyst-15</td>
<td>10</td>
<td>100</td>
<td>15</td>
<td>94</td>
<td>98</td>
<td>92</td>
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Table 1 continued

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<tr>
<th>B</th>
<th>Reaction Medium</th>
<th>Concentration</th>
<th>Conversion</th>
<th>Time (min)</th>
<th>% Yield</th>
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<tr>
<td>0.5 M DMSO</td>
<td>[NMP]CH₂S₃O₁</td>
<td>7.5 mol%</td>
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<td>SILnP</td>
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<td>130</td>
<td>30</td>
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<td>8.3 wt% Sulfolane</td>
<td>LiCl</td>
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<td>120</td>
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<td>120</td>
<td>100</td>
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<td></td>
<td></td>
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<td></td>
<td>86</td>
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<td>TiO₂</td>
<td>4.2 wt%</td>
<td>140</td>
<td>5</td>
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<td>10 wt% DMA</td>
<td>H₂SO₄-NaBr</td>
<td>6 mol%</td>
<td>100</td>
<td>120</td>
<td>-</td>
</tr>
<tr>
<td>0.3 M 9:1 (v/v) 1,4-dioxane/DM&lt;wbr&gt;SO</td>
<td>Amberlyst-15</td>
<td>-</td>
<td>110</td>
<td>3</td>
<td>98</td>
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<td>2 wt% Water/DHM THF</td>
<td>Amberlyst-70</td>
<td>0.07 wt%</td>
<td>130</td>
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<td>~85</td>
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<tr>
<td>3 wt% DMSO</td>
<td>Nafion(15)/MCF</td>
<td>0.1 mM H⁺</td>
<td>90</td>
<td>120</td>
<td>94</td>
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Table 2. Fructose dehydration in biphasic system.

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<th>Fructose Loading</th>
<th>Aqueous Phase</th>
<th>Organic Phase</th>
<th>Aq: Org Phase Ratio</th>
<th>Catalyst</th>
<th>Catalyst Loading (mequiv H+)</th>
<th>T° C</th>
<th>Time (h)</th>
<th>Conv (%)</th>
<th>Selectivity (%)</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1.2 M</td>
<td>Water</td>
<td>MIBK</td>
<td>1:9 (v/v)</td>
<td>Lewatit</td>
<td>SC102</td>
<td>7.5</td>
<td>88</td>
<td>72</td>
<td>47</td>
<td>34</td>
</tr>
<tr>
<td>0.16 - 1.1 M</td>
<td>Water</td>
<td>MIBK</td>
<td>1:5 (v/v)</td>
<td>H-ZSM5</td>
<td>2.5 - 16 mequiv H+</td>
<td>16</td>
<td>5</td>
<td>60</td>
<td>59</td>
<td>53</td>
</tr>
<tr>
<td>0.16 - 1.1 M</td>
<td>Water</td>
<td>MIBK</td>
<td>1:5 (v/v)</td>
<td>HY- Faujasite, Si/Al = 10</td>
<td>2.5 - 5 min</td>
<td>16</td>
<td>60</td>
<td>74</td>
<td>56</td>
<td>41</td>
</tr>
<tr>
<td>0.16 - 1.1 M</td>
<td>Water</td>
<td>MIBK</td>
<td>1:5 (v/v)</td>
<td>H- Mordenite, Si/Al = 11</td>
<td>2.5 - 5 min</td>
<td>16</td>
<td>60</td>
<td>76</td>
<td>91</td>
<td>69</td>
</tr>
<tr>
<td>30 wt% 7:3 (w/w)</td>
<td>Water/DMS O/PVP</td>
<td>MIBK/2-butanol</td>
<td>(w/w)</td>
<td>HCl</td>
<td>0.25 - 18 -3 pH 17 2.5</td>
<td>18</td>
<td>2.5</td>
<td>82</td>
<td>83</td>
<td>68</td>
</tr>
<tr>
<td>50 wt% 7:3 (w/w)</td>
<td>Water/DMS O/PVP</td>
<td>MIBK/2-butanol</td>
<td>(w/w)</td>
<td>HCl</td>
<td>0.25 - 18 -3 pH 17 2.5</td>
<td>18</td>
<td>2.5</td>
<td>92</td>
<td>77</td>
<td>71</td>
</tr>
<tr>
<td>10 wt% 1:1 (w/w)</td>
<td>Water/DMS O</td>
<td>MIBK/2-butanol</td>
<td>(w/w)</td>
<td>HCl</td>
<td>1.0 - 17 4 pH 0 mi</td>
<td>17</td>
<td>4</td>
<td>95</td>
<td>89</td>
<td>85</td>
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<tr>
<td>wt%</td>
<td>Water/NMP</td>
<td>wt%</td>
<td>THF</td>
<td>wt%</td>
<td>Water</td>
<td>wt%</td>
<td>Taa-SBA-15</td>
<td>wt%</td>
<td>Water</td>
<td>wt%</td>
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<tr>
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<tr>
<td>10</td>
<td>4:6 (w/w)</td>
<td>1:1</td>
<td>Resin</td>
<td>100</td>
<td>90</td>
<td>18</td>
<td>98</td>
<td>85</td>
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<td>50</td>
<td>4 h</td>
<td>-</td>
<td>-</td>
<td>60</td>
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<tr>
<td>30</td>
<td>Water</td>
<td>7:3</td>
<td>Taa-SBA-15</td>
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<td>18</td>
<td>30</td>
<td>66</td>
<td>74</td>
<td>58</td>
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<td>50</td>
<td>90</td>
<td>99</td>
<td>89</td>
<td>14</td>
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<td>B(OH)₃</td>
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<td>45</td>
<td>52</td>
<td>54</td>
<td>28</td>
<td>14</td>
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<td>30</td>
<td>Water</td>
<td>MIBK</td>
<td>B(OH)₃</td>
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<td>H-Mordenite</td>
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<td>11</td>
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<td>95</td>
<td>74</td>
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Table 3. Fructose dehydration in ionic liquids.

<table>
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<tr>
<th>Fructose loading</th>
<th>Solvent</th>
<th>catalyst</th>
<th>catalyst loading</th>
<th>T(°C)</th>
<th>Time</th>
<th>Yield(%)</th>
<th>ref</th>
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</thead>
<tbody>
<tr>
<td>0.5 M</td>
<td>[BMIM]BF4/DMSO</td>
<td>-</td>
<td></td>
<td>80</td>
<td>15 h</td>
<td>27</td>
<td>154</td>
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<tr>
<td>0.5 M</td>
<td>[BMIM]BF4/DMSO</td>
<td>-</td>
<td></td>
<td>80</td>
<td>32 h</td>
<td>36</td>
<td>154</td>
</tr>
<tr>
<td>0.5 M</td>
<td>[BMIM]BF4/DMSO</td>
<td>Amberlyst-15</td>
<td>88 g/L</td>
<td>80</td>
<td>32 h</td>
<td>75</td>
<td>154</td>
</tr>
<tr>
<td>0.5 M</td>
<td>[BMIM]BF4/DMSO</td>
<td>Amberlyst-15</td>
<td>175 g/L</td>
<td>80</td>
<td>32 h</td>
<td>87</td>
<td>154</td>
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<td>[BMIM]PF6/DMSO</td>
<td>Amberlyst-15</td>
<td>88 g/L</td>
<td>80</td>
<td>24 h</td>
<td>70</td>
<td>154</td>
</tr>
<tr>
<td>0.5 M</td>
<td>[BMIM]PF6/DMSO</td>
<td>Amberlyst-15</td>
<td>175 g/L</td>
<td>80</td>
<td>24 h</td>
<td>80</td>
<td>154</td>
</tr>
<tr>
<td>10 wt%</td>
<td>[EMIM]Cl</td>
<td>-</td>
<td></td>
<td>80</td>
<td>3 h</td>
<td>1</td>
<td>95</td>
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<tr>
<td>10 wt%</td>
<td>[EMIM]Cl</td>
<td>-</td>
<td></td>
<td>100</td>
<td>3 h</td>
<td>40</td>
<td>95</td>
</tr>
<tr>
<td>10 wt%</td>
<td>[EMIM]Cl</td>
<td>-</td>
<td></td>
<td>120</td>
<td>3 h</td>
<td>72</td>
<td>95</td>
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<tr>
<td>10 wt%</td>
<td>[BMIM]Cl</td>
<td>NHC-Cr</td>
<td>9 mol%</td>
<td>100</td>
<td>6 h</td>
<td>96</td>
<td>155</td>
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<tr>
<td>6.2 wt%</td>
<td>ChCl/Citric Acid</td>
<td></td>
<td></td>
<td>80</td>
<td>1 h</td>
<td>77.8</td>
<td>160</td>
</tr>
<tr>
<td>5 wt%</td>
<td>[BMIM]Cl</td>
<td>Amberlyst-15</td>
<td>5 wt%</td>
<td>120</td>
<td>1 min</td>
<td>82.2</td>
<td>161</td>
</tr>
<tr>
<td>5 wt%</td>
<td>[BMIM]Cl + 6 wt%</td>
<td>Amberlyst-15</td>
<td>5 wt%</td>
<td>25</td>
<td>6 h</td>
<td>78</td>
<td>158</td>
</tr>
<tr>
<td>5 wt%</td>
<td>[BMIM]Cl</td>
<td>GeCl4</td>
<td></td>
<td>10</td>
<td>100</td>
<td>5 min</td>
<td>92.1</td>
</tr>
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</table>
Table 3 continued

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Catalyst</th>
<th>Catalyst loading</th>
<th>T(°C)</th>
<th>Time</th>
<th>Yield(%)</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4M water</td>
<td>H₃PO₄</td>
<td>0.14M</td>
<td>176-189</td>
<td>20min</td>
<td>12.4</td>
<td>167</td>
</tr>
<tr>
<td>1.4M water</td>
<td>H₃PO₄/(NH₄)₂HPO₄</td>
<td>0.06M/0.076 M</td>
<td>174-180</td>
<td>20min</td>
<td>23</td>
<td>167</td>
</tr>
<tr>
<td>1:1(v/v) water/dioxane</td>
<td>H₃PO₄/pyridine</td>
<td>0.18M/0.6M</td>
<td>220-228</td>
<td>20min</td>
<td>46</td>
<td>167</td>
</tr>
<tr>
<td>2wt% water</td>
<td>TiO₂</td>
<td>50wt%</td>
<td>200(MI)</td>
<td>5min</td>
<td>19</td>
<td>170</td>
</tr>
</tbody>
</table>

Table 4. Glucose dehydration in monophasic system.

<table>
<thead>
<tr>
<th>Glucose loading g</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Catalyst loading</th>
<th>T(°C)</th>
<th>Time</th>
<th>Yield(%)</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4M water</td>
<td>H₃PO₄</td>
<td>0.14M</td>
<td>176-189</td>
<td>20min</td>
<td>12.4</td>
<td>167</td>
<td></td>
</tr>
<tr>
<td>1.4M water</td>
<td>H₃PO₄/(NH₄)₂HPO₄</td>
<td>0.06M/0.076 M</td>
<td>174-180</td>
<td>20min</td>
<td>23</td>
<td>167</td>
<td></td>
</tr>
<tr>
<td>2.8M water</td>
<td>H₃PO₄/pyridine</td>
<td>0.18M/0.6M</td>
<td>220-228</td>
<td>20min</td>
<td>46</td>
<td>167</td>
<td></td>
</tr>
<tr>
<td>2wt% water</td>
<td>TiO₂</td>
<td>50wt%</td>
<td>200(MI)</td>
<td>5min</td>
<td>19</td>
<td>170</td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Glucose Loading</th>
<th>Aqueous Phase</th>
<th>Organic Phase</th>
<th>A:O Phase Ratio</th>
<th>Catalyst</th>
<th>Catalyst Loading</th>
<th>T(°C)</th>
<th>Time(min)</th>
<th>Conv (%)</th>
<th>Select (%)</th>
<th>Yield (%)</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 wt% water</td>
<td>2-butanol</td>
<td>2-3(v/v)</td>
<td>Nb$_2$O$_5$</td>
<td>8 wt%</td>
<td>170</td>
<td>110</td>
<td>70</td>
<td>70%</td>
<td>70%</td>
<td>49%</td>
<td>146</td>
</tr>
<tr>
<td>6 wt% water</td>
<td>2-butanol</td>
<td>2-3(v/v)</td>
<td>Ta$_2$O$_5$</td>
<td>8 wt%</td>
<td>160</td>
<td>140</td>
<td>70</td>
<td>83%</td>
<td>58%</td>
<td>182%</td>
<td></td>
</tr>
<tr>
<td>30 wt% water</td>
<td>MIB K NaCl</td>
<td>1:4(v/v)</td>
<td>B(OH)$_3$</td>
<td>100 g/ L</td>
<td>150</td>
<td>300</td>
<td>41</td>
<td>34%</td>
<td>14%</td>
<td>147%</td>
<td></td>
</tr>
<tr>
<td>30 wt% water</td>
<td>MIB K</td>
<td>4:9(v/v)</td>
<td>Ag$<em>3$PW$</em>{12}$O$_{40}$</td>
<td>13.3%</td>
<td>130</td>
<td>240</td>
<td>90</td>
<td>64%</td>
<td>76%</td>
<td>149%</td>
<td></td>
</tr>
<tr>
<td>5 wt%$^a$ water</td>
<td>-</td>
<td>-</td>
<td>Cr[(DS)H$<em>2$P W$</em>{12}$O$_{40}$]$_3$</td>
<td>0.015 M</td>
<td>170</td>
<td>240</td>
<td>100</td>
<td>70%</td>
<td>70%</td>
<td>184%</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ MI, microwave irradiation. $^b$ Yields were based on combined EMF and HMF.

Table 5. Glucose dehydration in biphasic system.
Table 6. Glucose dehydration in ionic liquids.

<table>
<thead>
<tr>
<th>Glucose loading</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Catalyst loading</th>
<th>T(°C)</th>
<th>Time</th>
<th>Conv(%)</th>
<th>Select(%)</th>
<th>Yield(%)</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>5wt%</td>
<td>water- NaCl</td>
<td>SBP</td>
<td>1:2(w/w)</td>
<td>Nb/CB-2-DP</td>
<td>133w</td>
<td>170</td>
<td>120</td>
<td>78</td>
<td>26</td>
</tr>
<tr>
<td>5wt%</td>
<td>water- NaCl</td>
<td>SBP</td>
<td>1:2(w/w)</td>
<td>Nb/CB-1-DP</td>
<td>133w</td>
<td>170</td>
<td>120</td>
<td>34</td>
<td>52</td>
</tr>
<tr>
<td>6.5wt%</td>
<td>water MIB</td>
<td>K</td>
<td>1:3(v/v)</td>
<td>ZrPO</td>
<td>20wt</td>
<td>165</td>
<td>~360</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>6.5wt%</td>
<td>water MIB</td>
<td>K</td>
<td>1:3(v/v)</td>
<td>ZrPO/Si</td>
<td>20wt</td>
<td>165</td>
<td>~400</td>
<td>40</td>
<td>52</td>
</tr>
</tbody>
</table>

*Cellulose was used instead of glucose.*
<table>
<thead>
<tr>
<th>Percent</th>
<th>Ionic Liquid</th>
<th>Metal Compound</th>
<th>Time</th>
<th>Temperature</th>
<th>Yield</th>
<th>FTIR Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>20wt%</td>
<td>[EMIM]Cl Al(O\textsubscript{Pr})\textsubscript{3}</td>
<td>10 mol%</td>
<td>6h</td>
<td>140</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20wt%</td>
<td>[EMIM]Cl AlEt\textsubscript{3}</td>
<td>10mol%</td>
<td>6h</td>
<td>140</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>23wt%</td>
<td>[EMIM]Cl Cr-NP</td>
<td>10mol%</td>
<td>6h</td>
<td>140</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*a* microwave irradiation
CHAPTER 2: PRODUCTION OF 5-HYDROXYMETHYLFURFURAL FROM GLUCOSE USING A COMBINATION OF LEWIS AND BRØNSTED ACID CATALYSTS IN WATER IN A BIPHASIC REACTOR WITH AN ALKYLPHENOL SOLVENT

A paper published in ACS Catalysis, 2012, 2, 930−934

Yomaira J. Pagán-Torres, Tianfu Wang, Jean Marcel R. Gallo, Brent H. Shanks, James A. Dumesic*

[a] Tianfu Wang and Dr. Shanks designed the concept of using combination of Lewis acid (Ln) and Brosted acids and Tianfu carried out results in parallel to Yomaira’s aluminum work. Tianfu and Yomaira wrote the paper together and Tianfu was responsible for most of work in the supplemental information and additional work addressing the reviewer’s comments.

2.1. Abstract

We report the catalytic conversion of glucose in high yields (62%) to 5-hydroxymethylfurfural (HMF), a versatile platform chemical. The reaction system consists of a Lewis acid metal chloride (e.g., AlCl₃) and a Brønsted acid (HCl) in a biphasic reactor consisting of water and an alkylphenol compound (2-sec-butylphenol) as the organic phase. The conversion of glucose in the presence of Lewis and Brønsted acidity proceeds through a tandem pathway involving isomerization of glucose to
fructose, followed by dehydration of fructose to HMF. The organic phase extracts 97% of the HMF produced, while both acid catalysts remain in the aqueous phase.

2.2. Introduction

Biomass has been intensely investigated as a renewable feedstock for the production of chemicals and transportation fuels in view of economic, environmental, and political concerns associated with diminishing fossil fuel resources. The development of economically viable processes for the production of chemical intermediates from biomass-derived carbohydrates has become an important challenge for research in this area, such as the development of efficient processes for the production of the platform chemical 5-hydroxymethylfurfural (HMF).\textsuperscript{1} In this respect, HMF has been identified as a primary building block for the production of furanic polyesters, polyamides, and polyurethanes analogous to those derived from the petroleum polymer industry.\textsuperscript{2} HMF is produced from the acid-catalyzed dehydration of C\textsubscript{6}-sugars (i.e., hexoses). The formation of HMF is proposed to take place through the dehydration of a 5 member monosaccharide ring. Hence, fructose which contains 21.5% of furanose tautomers in aqueous solution can be converted to HMF more efficiently than glucose which contains 1% of furanose tautomers in aqueous solutions.\textsuperscript{3} Accordingly, while considerable efforts have focused on the production of HMF from fructose in high yields,\textsuperscript{1a,1c,d} a catalytic system that efficiently converts glucose to HMF in water has yet to be developed. Although glucose can be converted with low yields to HMF using Brønsted acids, the
yield to HMF can be increased significantly if glucose is first isomerized to fructose, and
fructose is then dehydrated to HMF.

While the dehydration of fructose is catalyzed by strong acids, the challenge for the
conversion of glucose to HMF is to find a catalytic system that can selectively isomerize
fructose to fructose in tandem with the dehydration reaction. Glucose isomerization
proceeds by hydrogen transfer from the C-2 to the C-1 position and from the O-2 to the
O-1 position of the \( \alpha \)-hydroxy aldehyde to form the \( \alpha \)-hydroxy ketone. The mechanism
of hydrogen transfer from the O-2 to the O-1 position of the aldose is by a proton transfer
between the electronegative carbonyl and hydroxyl groups, whereas the transfer of
hydrogen from the C-2 to the C-1 position may occur through a hydride ion, or in
alkaline conditions as a proton. Lewis acids and Brønsted bases are catalysts commonly
used for this reaction. However, basic catalysts typically lead to side reactions.
Recent studies have been published on the development of new processing strategies
focused on the isomerization of glucose to fructose with subsequent acid-catalyzed
dehydration of fructose to HMF. Lewis acid catalysts in ionic liquids have been shown to
be the most promising systems for the conversion of glucose to HMF. \(^{1c}\) Zhao, et al. first
reported HMF yields of 68-70\% in a system consisting of 1-ethyl-3-methyl-imidazolium
chloride and a \( \text{CrCl}_2 \) catalyst. \(^{1b}\) It is believed that the high activity and selectivity
observed for the production of HMF in ionic liquids with chromium catalysts are caused
by the stabilization of the transition state for ring opening of glucose by the Lewis acidic
Cr center during glucose isomerization. \(^{7}\) Other studies have been carried out on this same
reaction using different ionic liquids or Lewis acid catalysts. \(^{8}\) The main disadvantages of
using ionic liquids are that they are expensive and subject to deactivation by small
amounts of water formed during dehydration reactions. Binder, et al. reported that a
mixture consisting of dimethylacetamide (DMA), NaBr, and a Lewis acid, CrCl₂, could
reach HMF yields of 81%, being as effective as ionic liquid systems. Huang, et al.
reported an HMF yield of 63% from glucose by a two step process consisting of the
isomerization of glucose to fructose in the presence of glucose isomerase and borate ions,
followed by the acid catalyzed dehydration of fructose to HMF using HCl as a catalyst in
a biphasic system. Takagaki, et al. reported HMF yields of 42% at a 73% conversion by
a similar two step process by combining a solid acid catalyst, Amberlyst-15, and a solid
base catalyst, Mg-Al hydrotalcite, in N,N-dimethylformamide. Nikolla, et al. reported
HMF yields of 57% at 79% conversion of glucose using a Lewis acidic Sn-Beta zeolite
and HCl in a water/NaCl/THF biphasic reaction system. Recently, Abu-Omar et al.
reported an HMF yield of 61% from glucose using AlCl₃·6H₂O as the catalyst in a
biphasic system where THF was used as the extracting solvent.

In general, the conversion of glucose to HMF can follow two reaction pathways.
One pathway is through a Lewis acid catalyzed isomerization of glucose to fructose
combined with the dehydration of fructose to HMF (see Supporting Information Scheme
S1). The other pathway is through the direct dehydration of glucose to HMF (Scheme
S2). From these two reaction pathways the one passing through fructose should be more
selective towards HMF formation. Based on studies of the Lewis acid-catalyzed
isomerization of hexoses, one can hypothesize that the combination of Lewis and
Brønsted acidity could produce HMF by a combined isomerization/dehydration reaction of glucose to HMF, as illustrated in Scheme 1.

Scheme 1. Conversion of glucose to HMF by a combined isomerization/dehydration reaction pathway.

2.3. Results and Discussion

In this communication, we report the conversion of glucose to HMF in a biphasic reactor system in the presence of Lewis acid salts (AlCl₃, SnCl₄, VCl₃, InCl₃, GaCl₃, LaCl₃, DyCl₃ and YbCl₃). The biphasic reactor consists of an aqueous layer saturated with sodium chloride and an extracting organic layer consisting of 2-sec-butylphenol (SBP). Metal chlorides were dissolved in the aqueous layer, and the pH was adjusted to 2.5 by the addition of HCl, with the exception of SnCl₄ for which dissolution of the salt produced a solution with a pH of 1.8. The rationale for using a biphasic reactor is that the reactive HMF product can be continuously extracted from the acidic aqueous phase, thereby minimizing condensation reactions of HMF with glucose that lead to solid humins and rehydration reactions of HMF to form levulinic and formic acid.¹⁵ In this respect, we have recently identified that alkylphenol compounds are effective for the extraction of levulinic acid and furan compounds from acidic aqueous solutions.¹⁵ Thus, we employed this extracting solvent for the removal of HMF from the reactive aqueous
layer. Preliminary reaction kinetics of glucose dehydration with different metal chlorides as Lewis acid catalysts were also studied, which could provide more insight into the reaction mechanism and aid the rational design of bifunctional Lewis/Bronsted acid catalytic system for dehydration reactions in the future. Experiments for the conversion of glucose to HMF were performed at 443 K under autonomous pressure. The main products observed were fructose, HMF, and solid humins.

It can be seen in Table 1, entries 1-2, that glucose can be converted in the presence of the mineral acid, HCl, without any metal chloride catalyst; however, the selectivity for production of HMF is only 30% at 91% conversion. In the absence of an isomerization catalyst, the formation of HMF may follow a mechanism, in which the open-chain form of glucose is dehydrated at the C-2 position, forming a carbocation which reacts with the hydroxyl group at C-5 position, forming tetrahydro-3,4-dihydroxy-5-(hydroxymethyl)-2-furaldehyde followed by further dehydration to form HMF (see Supporting Information Scheme S2). The addition of a Lewis acid salt clearly leads to a significant increase in HMF selectivity, as shown in Table 1, entries 3-10. The presence of AlCl₃ leads to 68% HMF selectivity at 91% conversion, with a short reaction time. Moderate HMF selectivities of 53, 52 and 50% were obtained at conversions of 92, 86 and 90% for the addition of VCl₃, InCl₃ and GaCl₃, respectively to the aqueous layer. YbCl₃, DyCl₃ and LaCl₃ were also studied, displaying HMF selectivities of 46, 41 and 44%, respectively. The addition of SnCl₄ to the aqueous layer led to a glucose conversion of 90% with 58% selectivity to HMF; however, the pH of this solution was 1.8. At this same pH of 1.8, AlCl₃ generated a conversion of 90% with 68% selectivity to HMF.
The reaction effluent obtained using AlCl₃ as the Lewis acid catalyst (Table 1 entry 3) was analyzed by HPLC and Fourier Transform Ion Cyclotron Resonance (FT-ICR) mass spectrometry for the identification of byproducts. A 4% yield of levulinic acid was determined by HPLC, and disaccharides and levoglucosan were identified by FT-ICR. The formation of these products is in agreement with previous literature. In addition, insoluble humins were observed, these species being produced by the cross-polymerization of glucose and HMF.

Table 1. Conversion of glucose to HMF in a biphasic system with SBP as extracting organic layer.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conversion [%]</th>
<th>Selectivity [%]</th>
<th>Time [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>15</td>
<td>52</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>91</td>
<td>30</td>
<td>420</td>
</tr>
<tr>
<td>3</td>
<td>AlCl₃</td>
<td>91</td>
<td>68</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>SnCl₄</td>
<td>90</td>
<td>58</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>VCl₃</td>
<td>92</td>
<td>53</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>GaCl₃</td>
<td>90</td>
<td>50</td>
<td>120</td>
</tr>
<tr>
<td>7</td>
<td>InCl₃</td>
<td>86</td>
<td>52</td>
<td>150</td>
</tr>
<tr>
<td>8</td>
<td>YbCl₃</td>
<td>93</td>
<td>46</td>
<td>120</td>
</tr>
<tr>
<td>9</td>
<td>DyCl₃</td>
<td>93</td>
<td>41</td>
<td>160</td>
</tr>
<tr>
<td>10</td>
<td>LaCl₃</td>
<td>87</td>
<td>44</td>
<td>240</td>
</tr>
</tbody>
</table>
[a] Reaction conditions: 5 wt% glucose in water saturated with NaCl, reaction temperature of 443 K, organic to aqueous mass ratio of 2, pH = 2.5 with the exception of entry 4 which has a pH = 1.8. Entries 3-5, glucose to Lewis acid molar ratio of 67. Entries 6-10, glucose to Lewis acid molar ratio of 13.

Although typical Lewis acids, such as metal halides, are generally considered to be inactive in water, Fringuelli, et al.\textsuperscript{17} recently demonstrated that AlCl\textsubscript{3}, TiCl\textsubscript{4} and SnCl\textsubscript{4} are active in Lewis acid-catalyzed reactions in water at pH < 4. Metals salts can form different species depending on the pH of the aqueous solution. Aluminum, for example, can form the Keggin heteropolycation in alkaline aqueous solution, while it is present as solvated Al\textsuperscript{3+} at pH < 3.\textsuperscript{18} For SnCl\textsubscript{4}, the mononuclear species Sn(OH)\textsubscript{4-y}+(4-y)+ has been proposed primarily in cationic form in pH < 2.\textsuperscript{18-19} At the pH employed in this study, vanadium is present as VO\textsubscript{2}+, whereas all other metal ions are present as solvated cations.\textsuperscript{18} Fringuelli, et al.,\textsuperscript{17} have shown the pH of the solution plays a key role in controlling the Lewis acidity of metal halides in an aqueous solution. Therefore, in the system used in this work for glucose conversion to HMF, the acidic pH is responsible for the formation of the catalytically active metal species, thus facilitating glucose ring-opening and the subsequent dehydration reactions.

Figure 1 shows the conversion of glucose to HMF as a function of time in the presence of AlCl\textsubscript{3}, SnCl\textsubscript{4}, VCl\textsubscript{3}, GaCl\textsubscript{3}, InCl\textsubscript{3} and without the metal chloride. (See Figure S1 of the Supporting Information for reaction kinetics data upon addition of lanthanide salts.) In Figure 1A-B, fructose is observed to be a dominate intermediate which reaches a maximum concentration during the first 10 minutes of reaction in the presence of AlCl\textsubscript{3}.
and SnCl₄. At longer reaction times fructose is consumed with a concomitant formation of HMF. For reactions catalyzed by VCl₃, GaCl₃ and InCl₃, fructose is also produced as an intermediate (Figure 1C-E), but in lower quantities compared to AlCl₃ and SnCl₄. For the experiment performed in the absence of a Lewis acid salt (Figure 1F), fructose is not observed, suggesting that HMF is produced from the acid catalyzed dehydration of glucose. It is clear from Figure 1 that reaction systems with higher fructose quantities show higher HMF yields, as observed for AlCl₃ and SnCl₄ (Table 1 entries 3-4). For systems with lower rates of fructose formation, such as for the cases of VCl₃, GaCl₃, and InCl₃, the direct dehydration of glucose to HMF could have a significant contribution, leading to lower selectivities to HMF.

The effectiveness of the Lewis acids studied in this work for the conversion of glucose to fructose can be understood in terms of their intrinsic properties, such as the Lewis acid softness and ionic radius. For example, aluminum is the hardest of the Lewis acids studied, and it should interact strongly with the oxygen atoms of the hydroxyl groups in glucose, which are hard Lewis bases. Similarly, the ionic radius of the Lewis acid metal cations can be related to the reactivity of glucose. For example, the activity for glucose conversion and HMF formation increase with decreasing ionic radii from In³⁺ > Ga³⁺ > Al³⁺ and for the lanthanide series from La³⁺ > Dy³⁺ > Yb³⁺. The increased catalytic activity with decreasing ionic radius can be attributed to stronger electrostatic interaction between glucose and the smaller cations, caused by an increase in the effective surface charge density of the ion. Ionic radii for the cations studied can be found in the Supporting Information (Table S1).
The dehydration of fructose to HMF with high yields has been reported in previous studies using mineral acids and salts in a biphasic reactor with organic solvents such as tetrahydrofuran (THF), methyl isobutyl ketone (MIBK), and 2-butanol. In this study, THF showed the highest partitioning of HMF into the organic phase. Therefore, we have investigated the use of THF as the extracting organic layer in our reaction system. Results are shown in Table 2 for the production of HMF from glucose in a biphasic reactor using THF or SBP as the organic phase.

Figure 1. Glucose conversion in a biphasic system with HCl and (A) AlCl₃, (B) SnCl₄, (C) VCl₃, (D) GaCl₃, (E) InCl₃ and (F) no Lewis acid as a function of time. (■) Glucose, (○) Fructose, and (▲) HMF.
Figure 1 continued

Table 2. Comparison between extracting organic layers for the conversion of glucose to HMF in a biphasic reaction system using AlCl$_3$ and HCl as catalysts.[a]

<table>
<thead>
<tr>
<th>Extract</th>
<th>Conversion %</th>
<th>Selectivity %</th>
<th>HMF in Org %</th>
<th>HCl in Org %</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>80</td>
<td>71</td>
<td>93</td>
<td>30</td>
</tr>
<tr>
<td>SBP</td>
<td>88</td>
<td>70</td>
<td>97</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 5 wt% glucose in water saturated with NaCl, glucose to Lewis acid molar ratio of 67, pH = 2.5, reaction temperature of 443 K, organic to aqueous mass ratio of 2.

Using SBP as the extracting solvent led to an HMF yield of 62%, and 97% of the HMF produced was extracted to the organic layer. In contrast, when using THF as the extracting solvent, an HMF yield of 57% was obtained, and 93% of the HMF was extracted into the organic phase. In addition to the higher HMF yields obtained using SBP, an important advantage of the SBP solvent with this biphasic system is that none of the HCl was detected in the organic layer, in contrast to the system with THF in which 30% of the HCl was extracted into the organic layer. The extraction of mineral acid into
the organic solvent containing HMF can cause problems in further separation/purification steps, because of the high reactivity of HMF in the presence of acids.

To further demonstrate the effectiveness of the water-SBP biphasic system with AlCl₃ and HCl as catalysts in the conversion of glucose to HMF, experiments were conducted to assess the extent to which the acidic aqueous layer could be recycled for glucose conversion. For these experiments, four consecutive runs were carried out, each with a reaction time of 40 min. Between each run, the organic layer containing HMF was extracted, and fresh SBP and glucose were added to the acidic aqueous solution in the reactor. For the first run, the conversion and selectivity were those observed in Table 1 Entry 3. For consecutive experiments, no significant decreases in conversion and selectivity were observed, as shown in Figure 2.
Figure 2. Conversion and selectivity for production of HMF from glucose in consecutive runs using the same acidic aqueous solution containing AlCl$_3$ and HCl as catalysts. Reaction conditions: 5 wt% glucose in water saturated with NaCl, reaction temperature of 443 K, organic to aqueous mass ratio of 2, pH = 2.5, glucose to aluminum molar ratio of 67.

2.4. Conclusions

We have shown in this communication that HMF can be produced efficiently from glucose in a biphasic reactor system using SBP as the organic extracting layer in contact with an aqueous phase saturated with NaCl, at pH equal to 2.5, and containing Lewis acidic metal halides, such as AlCl$_3$. The overall yield of HMF is 62% in this biphasic system using AlCl$_3$ and HCl as catalysts. The presence of the Lewis and Brønsted acids allows the conversion of glucose to proceed through a tandem reaction pathway involving isomerization of glucose to fructose followed by dehydration of the latter to HMF.
In the biphasic system employed here, the organic phase extracts 97% of the HMF from the aqueous phase, while the Lewis and Brønsted acid catalysts (AlCl₃ and HCl, respectively) remain in the aqueous phase. This reaction system has significant advantages over existing systems, such as the recovery of the HMF produced by removal of the organic layer and recycle of the reactive aqueous layer. Considering that all of the HMF in the organic phase can be recovered, a purified HMF yield of 60% can be obtained. Although this yield is lower than that achieved using ionic liquids¹ᵇ and dimethylacetamide¹ᶜ as solvents and CrCl₂ as catalyst, our system avoids the use of expensive solvents and toxic salts. Furthermore, in these previous reaction systems, the yield of HMF is based on the reaction mixture, and further separation and purification of HMF from the reactive solution are required, leading to additional costs and product loss.

Supporting Information. Experimental section. Reaction schemes S1-S3 for the conversion of glucose to HMF. Figure S1 showing the conversion of glucose in the presence of YbCl₃, DyCl₃ and LaCl₃ as a function of time. Table S1 containing the ionic radii of cations. Table S2 showing HMIS rating for common organic solvent. This material is available free of charge via the Internet at http://pubs.acs.org.

Acknowledgement

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Enabling New Technologies Through Catalysis, CENTC, at the University of Washington, Seattle.

References


Supporting Information

PRODUCTION OF 5-HYDROXYMETHYLFURFURAL FROM GLUCOSE USING A COMBINATION OF LEWIS AND BRØNSTED ACID CATALYSTS IN WATER IN A BIPHASIC REACTOR WITH AN ALKYLPHENOL SOLVENT


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Content

1. Experimental Section

2. Reaction scheme for the conversion of glucose to HMF catalyzed by the combination of Lewis and Brønsted acid catalysts.

3. Brønsted acid catalyzed dehydration mechanism for the conversion of glucose to HMF.

4. Glucose conversion in a biphasic system with SBP in the presence of LaCl₃, DyCl₃, and YbCl₃ as a function of time.
1. Experimental Section

Biphasic dehydration reactions were carried out in 10 mL thick-walled glass reactors (Alltech) heated in an oil bath at 443 K. The oil temperature and magnetic stirring were controlled by an Isotemp digital stirring hotplate (Fisher Scientific). Preparation of the aqueous layer consisted of using solutions containing 5 mM AlCl$_3$, SnCl$_4$ or VCl$_3$ and adjusting their pH to 2.5 with HCl, with the exception of the 5mM SnCl$_4$, since a SnCl$_4$ solution at this concentration has a pH of 1.8. Solutions with 25 mM InCl$_3$, GaCl$_3$, LaCl$_3$, DyCl$_3$, or YbCl$_3$ were prepared and adjusted to a pH of 2.5. The pH-adjusted solutions were saturated with NaCl, and glucose was added to obtain a 5 wt% aqueous glucose feed. In a typical experiment, 1.5 g of the aqueous feed and 3.0 g of 2-sec-butylphenol (SBP) (Aldrich) were added to the reactor. The reactor was placed in the oil bath at 443 K and stirred at 1200 rpm. Reactors were removed from the oil bath at specific reaction times and cooled in a dry ice/ethylene glycol slurry. For recycle experiments, an aqueous solution with 5 mM AlCl$_3$ was first prepared and adjusted to a pH of 2.5 with HCl. This mixture was saturated with NaCl, glucose was added to reach 5 wt%, and 1.5 g of the aqueous feed was added to a 10 mL thick-walled glass reactor containing 3.0 g of SBP.
The reactor was heated in an oil bath to 443 K with stirring at 1200 rpm for 40 min. Upon completion of the reaction, reactors were cooled in a dry ice/ethylene glycol slurry. The organic layer was extracted and glucose added to the remaining aqueous layer to obtain a 5 wt% glucose mixture. Fresh SBP was added to the reactor, and the reaction was carried out for consecutive runs, as described above.

Experiments performed to compare SBP with THF as extracting organic layer were performed in a 50 mL pressure vessel (Hastelloy C-276, Parr Instrument). In a typical experiment, 8 g of the aqueous solution consisting of 5 wt% glucose and AlCl$_3$ (with a glucose to aluminum ratio of 67, adjusted to a pH = 2.5 and saturated with NaCl) were added to the vessel, followed by addition of 16 g of the organic layer. When THF was used as the extracting organic layer, the solvent was saturated with a NaCl-water mixture prior to contact with the aqueous feed mixture. The pressure vessel was sealed, stirred with a magnetic stir bar and heated with an external heating mantle to 443 K. The reactor was cooled in an ice bath upon completion of the reaction.

For all biphasic experiments, the organic and aqueous phases were separated and analyzed for quantification of glucose, fructose, and HMF by HPLC analysis. HPLC analysis was carried out using a Waters e2695 HPLC system equipped with a 2998 PDA UV detector (320 nm) and a 2414 refractive index detector maintained at 333 K. Aqueous layers were analyzed using an Aminex HPX-87H column (Biorad) at 353 K, using 0.005 M H$_2$SO$_4$ as the mobile phase at a flow rate of 0.6 mL min$^{-1}$. Organic layers were analyzed using a Waters 2695 HPLC system equipped with a 996 PDA UV detector and
a Zorbax SB-C18 reverse phase column (Agilent) at 308 K, using an acetonitrile:water gradient at a flow rate of 1 mL min$^{-1}$. Glucose and fructose were monitored using the refractive index detector, and HMF production was monitored using UV detectors (320 nm). Conversions are defined as the moles of glucose reacted divided by the moles of glucose fed. Selectivity to HMF was calculated as the moles of HMF produced divided by the moles of glucose reacted.

2. Reaction Scheme for the Conversion of Glucose to HMF Catalyzed by the Combination of Lewis and Brønsted Acid Catalysts.
Scheme S1. Reaction scheme for the conversion of glucose to HMF catalyzed by the combination of a Lewis and a Brønsted acid.¹
3. Brønsted Acid Catalyzed Dehydration Mechanism for the Conversion of Glucose to HMF.

Scheme S2. Reaction scheme for Brønsted acid catalyzed dehydration of glucose to HMF.²
4. Glucose Conversion in a Biphasic System with SBP in the Presence of LaCl₃, DyCl₃, and YbCl₃ as a Function of Time.

Figure S1. Glucose conversion and HMF production versus time in a biphasic system with SBP in the presence of LaCl₃, DyCl₃, and YbCl₃. (■) Glucose and (▲) HMF.
5. Table of the Ionic Radii of Cations.

Table S1. Ionic radii of cations.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Cation</th>
<th>Ionic Radius [pm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al\textsuperscript{3+}</td>
<td>68</td>
</tr>
<tr>
<td>Ga\textsuperscript{3+}</td>
<td>76</td>
</tr>
<tr>
<td>In\textsuperscript{3+}</td>
<td>94</td>
</tr>
<tr>
<td>Yb\textsuperscript{3+}</td>
<td>101</td>
</tr>
<tr>
<td>Dy\textsuperscript{3+}</td>
<td>105</td>
</tr>
<tr>
<td>La\textsuperscript{3+}</td>
<td>117</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Ions are 6-coordinate.\textsuperscript{3}

6. Identification of Side Products

In the conversion of monosaccharides to HMF, byproducts such as levulinic acid, formic acid, glucosaccharides, levoglucosan, soluble oligomers and polymers, and insoluble polymers (humins) are formed.\textsuperscript{4} While HMF, levulinic acid and formic acid, when present, can be identified and quantified by HPLC, the detection of other products requires more sophisticated techniques. Quantification of the soluble oligomers and
polymers is very difficult.\textsuperscript{4c,5} In addition, humins formed by cross-polymerization of 5-HMF and monosaccharide, can have different compositions at different reaction conditions.

6.1 HPLC

Experiments using AlCl\textsubscript{3} as the Lewis acid catalyst were used for quantification of byproducts. After reaction, both organic and aqueous layers were isolated and prepared for HPLC analysis, carried out with a Waters 1525 HPLC system coupled to a 2414 Refractive Index detector maintained at 333 K. Both organic and aqueous phase samples were analyzed using a Aminex HPX-87H column, with 5 mM H\textsubscript{2}SO\textsubscript{4} as the mobile phase at a flow rate of 0.6 mL min\textsuperscript{-1}. The only byproduct found by HPLC was levulinic acid, found mainly in the organic phase (SBP), while only a trace amount was detected in the aqueous phase. The calculated yield of levulinic acid was 4%.

6.2 Side Product Identification Using FT-ICR Mass Spectrometry

Analyses were performed on the organic and aqueous layers using Fourier Transform Ion Cyclotron Resonance (FT-ICR) mass spectrometry (Bruker) to identify byproducts having high molecular weights. Previous literature studies indicate that glucose reversion reactions could result in the formation of oligosaccharides or anhydrosugars from glucose by acid-catalyzed reactions.\textsuperscript{4} Similar results were observed in the mass spectra of our analysis, with disaccharides and levoglucosan being identified.
as side products. Scheme S3 shows the pathways for the formation of possible byproducts in the glucose conversion.

Scheme S3. Pathways for the formation of byproducts in glucose dehydration reactions.

7. Toxicity of 2-Sec-Butylphenol (SBP)

Table S2 shows HMIS ratings for SBP and other organic solvents commonly used in biphasic systems for conversion of monosaccharides to HMF. The HMIS health hazard rating is primarily based on the LC50 and LD50, which are relative, respectively, to inhalation and oral ingestion of a substance. If inhaled or ingested, SBP is more harmful
than tetrahydrofuran (THF), 2-butanol and toluene. In contrast, the vapor pressure of SBP is significantly lower than that of all other solvents shown in Table S2, thus in normal conditions of handling, the risk of inhalation of SBP is lower.

Table S2. HMIS rating for some common organic compounds used in biphasic reactions.[a]

<table>
<thead>
<tr>
<th>Organic Compound</th>
<th>Health hazard[b]</th>
<th>Vapor pressure[c] /mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>3</td>
<td>0.03</td>
</tr>
<tr>
<td>THF</td>
<td>2</td>
<td>143.0</td>
</tr>
<tr>
<td>Methyl isobutyl ketone</td>
<td>3</td>
<td>6.0</td>
</tr>
<tr>
<td>2-butanol</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>Toluene</td>
<td>2</td>
<td>22.0</td>
</tr>
</tbody>
</table>


[b] 4 = Extreme hazard; 3 = Serious hazard; 2 = Moderate hazard; 1 = Slight Risk; 0 = Practically non-toxic.

[c] At 20 °C.
8. References


CHAPTER 3: WATER-COMPATIBLE LEWIS ACID-CATALYZED
CONVERSION OF CARBOHYDRATES TO 5-HYDROXYMETHYLFURFURAL
IN A BIPHASIC SOLVENT SYSTEM


Tianfu Wang, Yomaira J. Pagán-Torres, Elliot J. Combs, James A. Dumesic, Brent H. Shanks*

3.1 Abstract

Water-compatible lanthanide-based Lewis acids for the efficient conversion of glucose and other carbohydrates to produce 5-hydroxymethylfurfural (HMF) were demonstrated in a biphasic reactor using sec-butyl phenol as the extracting solvent. The reaction of glucose dehydration to HMF was found to proceed under near-neutral conditions (pH=5.5) and a moderately high yield of 42 mol% could be obtained. The combined catalytic system also showed effectiveness to convert other polysaccharides to HMF. Furthermore, the aqueous phase was recycled and used for multiple times without significant loss of catalytic performance.
3.2 Introduction

As sustainability has become a widely recognized requirement for the chemical industry, a rapidly growing effort has been exploring the utilization of renewable carbon sources\(^{186}\). For truly sustainable carbon-based chemicals, the time scale on which the renewable carbon is generated must be the same as it is consumed and for this reason biomass represents a promising alternative to replace the current petroleum-based feedstock\(^{187}\). Carbohydrates accounts for 75\% of the 1.3 billion tons of non-edible biomass generated in the U.S. annually\(^ {188}\). One possible route to convert these carbohydrates to useful products is through the synthesis of 5-hydroxymethylfurfural (HMF), which has been suggested as a key biomass-derived chemical intermediate for the production of polymers\(^ {189,190}\), fine chemicals\(^ {191}\) and transportation fuels\(^ {192}\).

The C6 sugars, glucose and fructose, as well as oligomers and polymers with those as building species as monomers, such as starch and cellulose, have been used to produce HMF. The greatest extent of success has been achieved using fructose because it can be readily dehydrated to HMF using Bronsted acid catalysis\(^ {123,156,193,194}\). In contrast, glucose, which exists most extensively in the more stable glucopyranose form, is more difficult to dehydrate. However, it would be preferred to develop a process using glucose or polymers of it as the feedstock because glucose is more directly abundant and less expensive than fructose\(^ {194}\).

Given the fact that fructose has been shown to readily dehydrate to HMF, recent work on the conversion of glucose to HMF has focused on tandem strategies integrating
isomerization of glucose to fructose catalyzed by enzymes \(^{174}\), solid bases \(^{171}\) or solid acids \(^{195,196}\) with subsequent dehydration of fructose to HMF (Figure 1). Huang et al. \(^{15}\) performed a two-step reaction sequence in which the glucose was first isomerized to fructose in the presence of an added glucose isomerase enzyme and borate ion and then in the second step the fructose was dehydrated to HMF in a water-butanol biphasic system. By using this strategy, they obtained an overall HMF yield of 63.3%. Takagaki et al. \(^{16}\) reported HMF selectivities of 58% at glucose conversions of 73% using a combination of a solid base (Mg-Al hydrotalcite) and solid acid (Amberlyst-15) with N,N-dimethylformamide as the reaction medium. Nakajima et al. \(^{18}\) demonstrated that Nb\(_2\)O\(_5\)·nH\(_2\)O could catalyze glucose dehydration to HMF in water with HMF selectivities of 52% at a glucose conversion of 92%, although in their reaction the catalyst to substrate ratio was 10 on a mass basis. Recently, Nikolla et al. \(^{17}\) also reported HMF yields of 57% could be obtained by using the combination of a Lewis acid, Sn-Beta zeolite, and Bronsted acid, HCl, in a water-THF biphasic system. Additionally, metal chlorides have been demonstrated to function as Lewis acids in ionic liquids to catalyze glucose dehydration \(^{76,197}\). For example, Zhao et al. \(^{20}\) demonstrated that in the presence of CrCl\(_2\), an HMF yield of 68% directly from glucose could be achieved when using 1-ethyl-3-methylimidazolium chloride as the solvent.

These examples of bifunctional reaction systems for selective glucose conversion to HMF provide the basis to design new catalytic system that can carry out selective HMF production, but their utilization will require more understanding regarding the possible deactivation of the enzyme, the stability of hexose in the presence of base, the need for a
large excess of catalyst, the stability of zeolites in strongly acidic hot water, and the cost-effectiveness of using expensive ionic liquids including their susceptibility to water, which will be present in biomass processing. Water-compatible Lewis acids, on the other hand, have been proposed as a promising class of catalysts for the utilization of biomass to make chemicals and fuels\textsuperscript{198}. Recently, it has been shown that water-compatible Lewis acidic metal salts (homogeneous)\textsuperscript{199} and Sn-Beta zeolite (heterogeneous)\textsuperscript{200} catalyze the isomerization of glucose to fructose in aqueous solutions. In the Sn-Beta zeolite system, \textsuperscript{1}H and \textsuperscript{13}C NMR spectroscopy was used successfully to demonstrate that the catalyzed isomerization of glucose to fructose in water proceeded via a Lewis acid mediated intramolecular hydride shift. This result was consistent with previous literature in which Corma et al. also reported the Sn-Beta zeolite catalyzed Meerwein-Ponndorf-Verley (MPV) reduction of carbonyl compounds by alcohols\textsuperscript{201}. Furthermore, we reported that under suitable pH conditions, either moisture-sensitive metal salts (e.g. AlCl\textsubscript{3}) or water-compatible metal salts (e.g. LaCl\textsubscript{3}) were effective Lewis acids to catalyze the isomerization of glucose to fructose that could be combined with a Bronsted acid for subsequent dehydration of the fructose to realize high yields of HMF\textsuperscript{199}.

While a low solution pH is required for most conventional Lewis acid salts to maintain their Lewis acidity in the presence of water, we will discuss in the present study the conversion of glucose to HMF catalyzed by a series of lanthanide metal salts (LaCl\textsubscript{3}, DyCl\textsubscript{3} and YbCl\textsubscript{3}) that have been shown to function as water-compatible Lewis acids under a wide range of pH values (1.5, 2.5, 3.5, 4.5 and 5.5)\textsuperscript{202}. Operation at higher pH is quite desirable to minimize the use of strong mineral acids (HCl), which will mitigate
both materials of construction and environmental problems for industrial processes\textsuperscript{203}. Previous work has compared different lanthanide metal salts in aqueous systems and while the overall yield of HMF were quite low it was demonstrated that decreasing glucose reactivity to HMF occurred with increasing ionic radii from Yb to Dy to La, which was attributed to the larger cations having weaker electrostatic interaction with the glucose molecule\textsuperscript{147,204}. Therefore, the current study examines different lanthanide chloride salts in a biphasic reactor system under different pH conditions.

\textbf{Figure 1.} Scheme of glucose conversion to HMF via a tandem pathway

![Scheme of glucose conversion to HMF via a tandem pathway](image)

3.3. Experimental Section

3.3.1 Preparation of Reaction Solution

25mM LaCl\textsubscript{3}, DyCl\textsubscript{3}, and YbCl\textsubscript{3} (Aldrich) aqueous solutions were made by adding the appropriate amount of LnCl\textsubscript{3} into nanopure water and adjusting the pH to the targeted value by the addition of HCl. The pH value of the solution was measured using a combined glass electrode (6.0233.100, Metrohm) attached to a Metrohm 798 MPT Titrino automatic titrator. The as-made solutions were then saturated with NaCl.
3.3.2 Biphasic Reaction Conditions

The glucose (Fisher) dehydration reactions in the biphasic reaction system were carried out in a 10 ml thick-walled glass reactor (Alltech). An oil bath was used to heat the reactor rapidly to the desired reaction temperature (443K), with temperature and stirring being controlled by an Isotemp digital, stirring hotplate (Fisher Scientific).

In a typical experiment, 1.5 g of aqueous metal salt solution and 3.0 g of sec-butyl phenol (SBP) were added to the Alltech reactor. A triangularly-shaped stir bar was also added to allow for agitation. The reactor was then immersed in the oil bath at 443 K and stirred at 350 rpm. At specified times, the reactors were removed from the oil bath and then cooled in an ice bath to quench the reaction. For the recyclability experiments, an aqueous solution with 25 mM YbCl$_3$ was adjusted to a pH of 5.5 with HCl and saturated with NaCl. Glucose was then added to reach the 5 wt% level. 2.5 g of the aqueous solution and 5.0 g of SBP were added to a 10 ml thick-walled glass reactor. The reactor was immersed in an oil bath (443K) and stirred at 350 rpm for 80 min. After the reactors were cooled, the aqueous and organic phases were separated for further use. Aliquots were drawn from both the aqueous phase and organic phase to prepare samples for HPLC analysis. The remaining aqueous phase portion was weighed and then sufficient fresh glucose was added to obtain a roughly 5 wt% glucose mixture. This mixture and fresh SBP were added to the reactor, and the reaction was carried out for consecutive runs with the same conditions as described above. Reactions on other carbohydrates, maltose (Fisher), cellobiose (Fisher), starch (Fisher) and cellulose (MP Biomedicals), were
carried out with an aqueous solution of 25 mM YbCl$_3$ with solution pH of 5.5 using HCl and saturated with NaCl. The carbohydrates were added to 1.5 g of the aqueous phase to reach a 5 wt% level. The aqueous phase was then combined with 3.0 g of SBP and added to the Alltech reactor. The reactor was immersed in an oil bath (443K) and stirred at 350 rpm for 80 min.

3.3.3 Sample Analysis

For all of the biphasic experiments, the organic and aqueous phases were separated and aliquots were withdrawn for quantitative analysis of glucose and HMF by HPLC. HPLC analysis was performed using a Waters 1525 HPLC system equipped with a 2998 PDA UV detector (280 nm) and a 2414 refractive index detector maintained at 333 K. The aqueous phase samples were analyzed using a PL Hi-Plex H-form carbohydrate column at 353 K, using 5 mM H$_2$SO$_4$ as the mobile phase at a flow rate of 0.6 ml min$^{-1}$. The organic phase samples were analyzed using a Zorbax SB-C18 reverse phase column (Agilent) at 308 K, with a methanol:water (8:2 v/v) mixed solvent at a flow rate of 0.7 ml min$^{-1}$. Glucose disappearance was monitored using the refractive index detector, and the HMF production was monitored using the UV detector (280 nm). The definitions being used in the results and discussion section include: the conversion of glucose is defined as the moles of glucose reacted divided by the moles of initial glucose; the selectivity of HMF is defined as the moles of HMF produced divided by the moles of glucose reacted; and the yield of HMF is defined as the glucose conversion times the HMF selectivity.
3.4. Results and Discussion

A series of different lanthanide chloride salts, LaCl$_3$, DyCl$_3$ and YbCl$_3$, were tested for their glucose conversion to HMF reaction in a biphasic system. The aqueous phase was composed of the LnCl$_3$ salts, 5 wt% glucose, HCl (to adjust the solution pH to the desired value) and NaCl. It had been previously reported that the addition of NaCl to level of saturation in the aqueous phase was effective for increasing the partitioning of HMF into the organic phase$^{205}$, and so the same approach was used in this study with using a NaCl saturated aqueous solution. The organic phase was composed of sec-butyl phenol, which was recently demonstrated as an exceptionally effective solvent to extract more than 95% of the HMF produced thereby minimizing the undesired side-reactions of HMF in the aqueous phase. These side reactions lead to the condensation products of soluble species or insoluble species as well as the rehydration products of levulinic and formic acid$^{156}$. All of the reactions were run at 443 K and autonomous pressure with a stirring rate of 350 rpm.

The results for the glucose dehydration to HMF reaction are summarized in Table 1. As shown in entries 1 and 2, in the absence of lanthanide salts and under pH values approaching neutral condition (pH=5.5), glucose could be successfully converted to HMF over extended time in the biphasic reaction system. However, the use of the lanthanide chloride salts as an isomerization catalyst in the aqueous phase significantly enhanced the reactivity of glucose and led to higher yields of HMF. For example, it can be seen from entries 7, 9 and 10 that HMF selectivities of 45, 44, and 46 mol% could be obtained at glucose conversions of 88 mol% with YbCl$_3$, 89 mol% with DyCl$_3$, and 86 mol% with
LaCl$_3$, respectively. In the absence of any lanthanide chloride salt, the glucose conversion only reached 45 mol% even after 240 min of reaction (entry 2), in contrast to the conversions of about 90 mol% for reaction times of 80, 120, and 200 min with YbCl$_3$, DyCl$_3$, and LaCl$_3$, respectively. Since YbCl$_3$ appeared to be the most effective catalyst in the near-neutral condition (pH=5.5), it was further tested for glucose conversion under a wider range of pH values from 1.5 to 5.5. As shown from entries 4-7, the combination of YbCl$_3$ and HCl resulted in fairly similar glucose conversion levels and HMF selectivities when the reaction was allowed to progress for 80 min. At the lower pH value of 1.5 the glucose conversion rate was significantly higher, so the reaction was stopped after 40 min to achieve a conversion level close to that found for the higher pH levels. The slightly lower HMF selectivity observed for pH=1.5 could be due to either higher rates for non-selective reactions or could be due to the higher conversion rate causing the HMF mass transfer to the organic phase not being sufficiently rapid to counter balance its rate of production. Since the results for pH values from 2.5 to 5.5 were similar, a further experiment was performed using a higher YbCl$_3$ concentration. As shown in entry 8, increasing the concentration of YbCl$_3$ from 25 mM to 100 mM while keeping the pH at 5.5 resulted in an HMF selectivity of 46 mol% at a glucose conversion of 91 mol% at a shorter reaction time of 40 min thereby demonstrating that a more concentrated YbCl$_3$ would facilitate the catalytic transformation.

In general, metal halide salts have been classified as moisture-sensitive salts or water-compatible salts when they are subjected to aqueous media. Metal salts can react with water to form different species. On the one hand, typical Lewis acids commonly
used in organic media, such as AlCl₃ and TiCl₄, are usually considered to be ineffective Lewis acid in water because they readily hydrolyze to form inactive species. Fringuelli, et al. recently have demonstrated that the pH value of the aqueous solution plays a key role in controlling the effectiveness of the Lewis acids. In their report, they have shown that for low pH values in aqueous media, e.g., pH<4 for AlCl₃ and pH<1.5 for SnCl₄, all of the metal chlorides that were examined were active in carrying out Lewis acid-catalyzed organic transformations. Additionally, Kobayashi, et al. have demonstrated that lanthanide-based metal salts could function as water-compatible Lewis acids in water when used to catalyze the aldol reaction between silyl enol ethers and aldehydes in commercial aqueous formaldehyde solutions in THF. The fact that the lanthanide chloride salts examined in the current study could function as effective Lewis acids at pH=5.5 in the catalysis of the glucose dehydration reaction to HMF could be attributed to their existence as active Lewis acidic aqua ion species under the conditions used due to their high pKₐ values between 7.6 and 8.5.

The isomerization of the aldose-ketose has been reported as a mechanistically interesting reaction which proceeds through the transfer of hydrogen atom from C-2 and O-2 to C-1 and from O-1 of an α-hydroxy aldehyde to form the corresponding α-hydroxy ketone. The Lewis acid-mediated glucose to fructose isomerization in water has been demonstrated, by the coupling of kinetic isotopic labeling and NMR spectroscopy, to proceed via hydride transfer from C-2 to C-1. Since lanthanide-based Lewis acids are well-known for their strong affinity towards the carbonyl and hydroxyl species, we hypothesized that in our catalytic system, the glucose initially underwent an
isomerization reaction to form fructose mediated by lanthanide-based Lewis acids that was subsequently followed by dehydration of fructose to HMF. A proposed mechanism for the reaction is shown in Figure 2.

**Figure 2.** Proposed mechanism of lanthanide Lewis acid-mediated intra-molecular hydride shift in glucose/fructose isomerization and subsequent fructose dehydration to HMF. (Ln = lanthanide metal center)

The glucose conversion activities for YbCl$_3$, DyCl$_3$, and LaCl$_3$ are shown in Table 1 by comparison of entries 7, 9 and 10 with the rate increasing from LaCl$_3$ to DyCl$_3$ to YbCl$_3$, which is in accordance with the decrease in their ionic radius that is known as the lanthanide contraction $^{198}$. The differences in the catalytic effectiveness displayed between the different lanthanide metal centers could be understood using the hard-soft acid-base (HSAB) principle and effective surface charge density $^{147,210}$. As the ionic
radius of the cations decrease, they become less polarizable with more highly localized
charges and according to the HSAB principle would be deemed “harder” acids. The
carbonyl and hydroxyl groups present in glucose are generally considered hard bases and
as such the interaction between the glucose and lanthanide ions would be expected to be
stronger with decreasing ionic radius. Also, for the same level of charge (+3 for all three
cations used in the study), the interaction between glucose and the smaller cations would
be stronger due to their larger surface charge density \(^{147, 210}\).

Table 1. Results of glucose conversion to HMF in a biphasic reactor.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Catalyst concentration [mM]</th>
<th>Conditions pH</th>
<th>Conversion [mol%]</th>
<th>Selectivity [mol%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N/A</td>
<td>N/A</td>
<td>pH=5.5</td>
<td>20</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>N/A</td>
<td>N/A</td>
<td>pH=5.5</td>
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<td>53</td>
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Reaction conditions: 5 wt% glucose in nanopure water saturated with NaCl, pH adjusted with HCl, reaction temperature of 443 K, organic/aqueous mass ratio= 2 with 2-sec-butyl-phenol used as the organic layer to extract HMF from the aqueous phase. The experiments are repeated three times to gain the error bars.

The effectiveness of YbCl$_3$ in a pH=5.5 aqueous solution for the HMF production from other carbohydrates, e.g., maltose, cellobiose, starch and cellulose, was also examined. As shown from the results summarized in Figure 3, the HMF yields for starch, cellobiose and maltose that were 42, 40, and 31 mol%, respectively, were similar to the yield obtained from glucose (42 mol%) under the same reaction conditions. However, for the cellulose reaction the yield of HMF after 120 min was only 8 mol%, probably due to the slow hydrolysis associated with the strong $\beta$-1,4-glycosidic bonds present in the crystalline solid cellulose structure such that the liberation of the monosaccharide unit for subsequent dehydration to produce HMF would be difficult. Indeed, when the reaction time was prolonged to 360 min, an HMF yield of 21 mol% from cellulose was obtained. Although the yield of HMF directly from cellulose was moderately low compared with the other studied carbohydrates, converting cellulose directly to HMF could still be desirable due to the high abundance and low relative cost for cellulose.
**Figure 3.** Yields of HMF resulting from the conversion of different carbohydrates; reaction conditions: 5 wt% carbohydrate in water saturated with NaCl, reaction temperature of 443 K, organic to aqueous mass ratio of 2, pH = 5.5, YbCl$_3$ concentration of 25mM, reaction time of 80 min except for cellulose, which had a reaction time of 360 min.

To further explore the practicality of using the biphasic reaction system with combined Lewis and Bronsted homogeneous catalysts, experiments were performed to test the reusability of the biphasic system with YbCl$_3$ as the catalyst. In these experiments, after each reaction (80 min) was completed, aliquots from both the organic and aqueous phases were withdrawn for glucose and HMF analysis, then the aqueous phase was recycled and combined with additional glucose and a fresh organic SBP phase. The reaction was then performed again using the same condition as the first cycle. As shown in Figure 4, no significant losses in the glucose conversion or the HMF selectivity...
were observed for three consecutive cycles, suggesting that the biphasic catalytic system appeared to be recyclable.

**Figure 4.** Recyclability of the YbCl$_3$ biphasic reaction system; reaction conditions: 5 wt% glucose in water saturated with NaCl, reaction temperature of 443 K, organic to aqueous mass ratio of 2, pH = 5.5, YbCl$_3$ concentration of 25mM, and reaction time of 80 min.

3.5. Conclusions

Lanthanide-based water-compatible Lewis acid salts were found to be effective in converting glucose and other carbohydrates to produce HMF at moderately high yields (42 mol%). The system is promising due to the fact that it could even catalyze the reaction under near-neutral condition (pH=5.5), which would minimize the amount of
corrosive mineral acids such as HCl that would be needed. Sec-butyl phenol was found to be an exceptionally efficient solvent to extract most of the HMF produced from the aqueous phase into the organic phase to protect HMF from further degradation. Since most of the HMF was extracted into the organic phase, the system would provide improved opportunity for subsequently converting the HMF produced into useful chemicals or fuels. Additionally, it was found the biphasic reaction system could utilize other carbohydrates, including the cellulose, to produce HMF demonstrating the effectiveness of the catalytic system towards different feedstocks. Furthermore, the reactive aqueous phase could be recycled to catalyze the conversion of glucose to HMF multiple times without a significant loss in either glucose conversion or HMF selectivity.

Acknowledgements

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CHAPTER 4: KINETICS AND INSIGHTS INTO GLUCOSE DEHYDRATION CATALYZED BY HOMOGENEOUS LEWIS ACIDIC METAL SALTS IN WATER

A paper to be submitted to ACS Catalysis

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4.1 Abstract

Dehydration of glucose in the presence of various Lewis acidic metal salts was studied with water as reaction media. The glucose conversion kinetic profile was used to reflect the Lewis acid character of different metal ions. It was found that the pH value of the aqueous solution played an important role in controlling the Lewis activities. For the lanthanide chlorides, their Lewis acidity was comparable under the pH values studied (from 2.5 to 5.5). However, the Lewis acidity strength of other metal salts, such as aluminum chloride, showed dependence on the pH value of the solution. Activation energies with various Lewis acids were also calculated with both glucose and fructose to obtain more insight about the strength of the catalyst-substrate interaction as well as the dehydration reaction. The kinetic isotope effect with labeled glucose molecules was also studied to explore a more mechanistic understanding of the dehydration, which likely involves the 2-H atom of the glucose molecule in the transition state.
4.2. Introduction

Carbohydrates represent a promising energy and carbon source, since they account for 75% of the renewable and abundant biomass feedstock. As such, the development of efficient and economical processes that can convert carbohydrates to useful chemical intermediates is very desirable. 5-hydroxymethyl furfural (HMF), has been identified by the United States Department of Energy (US DOE) as one of the top 12 platform chemicals, having the potential to be a building block in synthesizing furanic-based polyesters, polyamides, and polyurethanes analogous to petroleum-based terephthalic acid. 37, 190, 211, 212, 213

HMF can be produced from C₆ carbohydrates (glucose and fructose) using acid catalysts. In the past decade, considerable effort has focused on the production of HMF from fructose with high yields. However, the more abundant and economical monosaccharide found in nature, glucose, is preferred as the feedstock. The lesser success in converting glucose to HMF is due to the stability of the pyranose ring structure. Therefore, several research groups have developed a tandem reaction pathway where glucose is first isomerized to fructose, followed by subsequent dehydration of fructose to HMF.

In order to implement the tandem isomerization-dehydration strategy to get high yields of HMF, researchers have focused on utilizing enzymes, solid bases or zeolites as isomerization catalysts with Brønsted acid catalysts for the dehydration reaction. Huang et al. reported high HMF yields of 63% from glucose using a two-step process consisting
of glucose isomerase and borate ions in aqueous media, followed by fructose dehydration with HCl to HMF in a biphasic system. Takagaki et al. reported HMF yields of 42% at 73% conversion by a similar two step process, using Mg-Al hydrotalcite as a solid base to isomerize glucose to fructose and Amberlyst-15 as a solid acid to dehydrate fructose, in a reaction media of N,N-dimethylformamide. Solid Lewis acid zeolites, such as Sn-Beta, have been used as metalloenzyme-like catalysts to isomerize glucose to fructose with high activity. Nikolla et al. later reported HMF yields of 57% from glucose using a combination of Sn-Beta zeolites and HCl in a biphasic reaction system. In addition to carrying out the reaction in aqueous or organic solvents, considerable efforts have focused on using ionic liquids as the solvent. For example, Zhao et al. reported HMF yields of 68-70% using 1-ethyl-3-methyl-imidazolium chloride as a solvent with a CrCl\(_2\) catalyst. The authors attributed the high activity and selectivity observed for the system to the facile ring opening of glucose and the stabilization of the transition state by Cr as a Lewis acid center.

Recently, various Lewis acidic metal salts, including Al\(^{3+}\), Ga\(^{3+}\), In\(^{3+}\), Sn\(^{4+}\), La\(^{3+}\), Dy\(^{3+}\), Yb\(^{3+}\), Zn\(^{2+}\), Ge\(^{4+}\), Cr\(^{3+}\), Cr\(^{2+}\), Cu\(^{2+}\), have been reported as active catalysts to convert C\(_5\) or C\(_6\) aldose sugars (glucose or xylose) to furanics in an aqueous media, organic solvents, or ionic liquids. Most of these reports have similarly focused on integrating the Lewis acid properties of the metal as the coordination center for glucose isomerization, and the protons resulting from the metal hydrolysis as a Brønsted acid to catalyze the dehydration reaction in order to achieve high yields of the furanic compounds. For example, a high HMF yield of over 60% was achieved by using a
combination of AlCl$_3$ and HCl in a one-pot biphasic system as reported independently by two research groups.$^{81, 83}$ However, to the best of our knowledge, there is no study in the literature to systematically tune the reaction conditions such as Lewis acidic metal type, pH values of the reaction media, temperature, etc. As a result, a comprehensive evaluation of intrinsic kinetic values, such as activation energies and turnover numbers so as to understand the Lewis acidic metal catalysts would provide valuable insight into how the acidic features affect the reaction results.

It is generally known that when metal chlorides are contacted with water, depending on their pK$_{\text{a}}$ hydrolysis constant values, they can be classified as either “water-compatible” or “water-sensitive” categories. Kobayashi et al. extensively studied using “water-compatible” Lewis acids represented by lanthanide trifluoromethanesulfonates, Ln(OTf)$_3$ to facilitate various organic transformations such as C-C and C-O bond formations.$^{219}$ The Lewis activity of Ln(OTf)$_3$ was ascribed to the high pK$_{\text{a}}$ values of the Ln cations, between 7.6 and 8.5, leading to their existence as coordinately unsaturated Lewis acidic aqua ions, which were believed to be the catalytically active species. Also, exchange rate constants for the substitution of inner-sphere water ligands or the water exchange rate constant (WERC) have been suggested to play a role in controlling the Lewis acidity of metal ions in water. Historically, it is thought that Lewis acidic metal salts, such as AlCl$_3$, are inactive in aqueous solutions, due to their favorable formation of mononuclear and polynuclear species in the presence of water molecules. Studies have shown that the speciation of these metal cations in water is highly dependent on the concentration of the metal cation and the solution pH.$^{206, 207}$ In this regard, metal salts
such as AlCl$_3$ and SnCl$_4$ are efficacious water-compatible Lewis acids along with other metals that can be active in water if used at a suitable pH.

We have recently reviewed the catalytic dehydration of C$_6$ sugars to HMF and concluded that strategies combining Lewis acid-catalyzed isomerization and Brønsted acid-catalyzed dehydration steps to convert glucose to HMF in either a biphasic system or in ionic liquid “one-pot” reactor configuration seem to be quite promising. Although many reports have focused on the efficacy of such systems on the overall conversion and selectivity, there have been limited studies performed to examine the kinetic profiles for the isomerization/dehydration steps. Better kinetic information can provide insights into the optimal ratio for the two catalytic functions as well as process and reactor conditions to optimize HMF production. Additionally, since many of the Lewis acids readily hydrolyze in water, which can either be the solvent or be produced during reaction, studies that can distinguish Brønsted and Lewis acidity and their effect on the catalytic process are necessary. In the current study, the effect of the nature of the Lewis acidic metal salts and different initial solution pH values on conversion kinetics of glucose were explored by examining Al, Ga, and In, which are hydrolysable Lewis acids and La, Dy, and Yb, which are water-compatible Lewis acids, for their activity in glucose dehydration at solution pH values ranging from 2.5 to 5.5. By studying the effects of these acids under the same initial pH conditions, the intrinsic effect of Lewis acid strength on the glucose dehydration kinetic profile could be determined. In addition, by calculating the activation energies between 150–170 °C, the observed activities could be related to the proposed reaction mechanism. Mechanistic studies have been performed by Davis and co-workers.
on the Sn-Beta type solid Lewis acid for glucose conversion in water and they concluded glucose/fructose isomerization proceeded through a C2 position hydride shift mechanism. To test whether the same mechanism occurs with homogeneous metal salt type Lewis acids, we also examined the kinetic isotope effect with labeled glucose molecules at the 2-H position.

4.3. Experimental

4.3.1 Preparation of Reaction Solution

Two types of Lewis acid salt solutions were prepared for reaction testing: water-compatible lanthanide metal salts and water-sensitive (hydrolysable) salts (e.g. AlCl3). For the lanthanide metal salts, 25mM LaCl3, DyCl3, or YbCl3 (Aldrich) aqueous solutions were made by adding the appropriate amount of LnCl3 into nanopure water (18 MΩ cm) and adjusting the pH to the targeted value though the addition of HCl. Similarly, 5mM AlCl3 or 25 mM InCl3 or GaCl3 (Aldrich) aqueous solutions were prepared by the same protocol. The pH value of the solutions were measured using a combined glass electrode (6.0233.100, Metrohm) attached to a Metrohm 798 MPT Titrino automatic titrator. The as-made solutions were then saturated with NaCl for further use. Glucose and fructose were purchased from Fisher Scientific as ACS Certified grade and used as received.

4.3.2 Biphasic Reaction Conditions

The glucose and fructose dehydration reactions in the biphasic reaction system were carried out in 10 ml thick-walled glass reactors (Alltech). An oil bath was used to heat the
reactor rapidly to the desired reaction temperature (443K), with temperature and stirring being controlled by an Isotemp digital stirring hot plate (Fisher Scientific).

In a typical experiment, 1.5 g of an aqueous metal salt solution containing 5 wt% of glucose or fructose and 3.0 g of organic extracting solvent, sec-butyl phenol (SBP) were added to the Alltech reactor. A triangular stir bar (Fisher Scientific) was also added to allow for adequate agitation. The reactor was then sealed with PTFE liner covered caps (Fisher Scientific) and immersed in the oil bath at 170 °C and stirred at 350 rpm. At specified times, the reactors were removed from the oil bath and then cooled rapidly in an ice bath to quench the reaction. For all the reactions, significant amounts of soluble and insoluble brownish humins were formed, of which the production rate was difficult to quantify. As with previous literature reported, the humin formation precluded a closed carbon balance analysis and thus the only product analyzed was HMF.

4.3.3 Effect of pH on the Activities of Different Lewis Acidic Metal Chloride Salts

Experiments were performed to study the pH effect on the activity of the different Lewis acid metal salts. YbCl$_3$ (25mM) was chosen to represent the water-compatible Lewis acids and AlCl$_3$ (5mM) was chosen for the water-sensitive Lewis acids. In either case, aqueous solutions were made and the pH was adjusted to 2.5, 3.5, 4.5 or 5.5. The same experimental procedure as described in section 2.2 was conducted with each of the solutions using a reaction temperature of 170°C. Considering the relatively small size of the reaction vial, rapid heat transfer was assumed and as such no time delay was used for the kinetic profiles.
4.3.4 Activation Energies, Catalyst Concentration Studies and Kinetic Isotope Effects (KIEs)

The kinetic experiments to determine the activation energies for LaCl$_3$, DyCl$_3$, YbCl$_3$, AlCl$_3$, InCl$_3$, and GaCl$_3$ were performed at 150, 160 and 170°C in the same experimental setup described in section 2.2 (for all the experiments, the pH was kept at the same value of 2.5). The glucose conversion profiles were analyzed for each metal chloride under the different temperatures and the activation energies were calculated accordingly assuming first order kinetics for the carbohydrate concentration. Experiments were also performed to study the effect of the Lewis acid metal salt concentration on glucose conversion. These experiments were performed for both YbCl$_3$ and AlCl$_3$ as the catalysts. Kinetic isotope effect (KIE) studies were carried out for both glucose and 2-D glucose (98%, CIL) in the presence of AlCl$_3$ as the catalyst and at the reaction temperature of 170 °C.

4.3.5 Kinetics Studies with Fructose as Feedstock

Fructose was also used as feedstock to provide complimentary information for the glucose dehydration reaction. Three different types of catalysts, AlCl$_3$ (5mM), YbCl$_3$ (25mM) and HCl were used to catalyze the fructose dehydration reaction under the biphasic experimental condition. For all three catalysts, a same pH value of 2.5 was used with a lower reaction temperature of 160 °C, since fructose was a more reactive substrate than glucose. Activation energies studies were also performed with the water-compatible
lanthanides (LaCl$_3$, DyCl$_3$, and YbCl$_3$) to gain more insight in fructose dehydration. For each LnCl$_3$, three different temperatures (150, 160 and 170°C) were used.

4.3.6 Sample Analysis

For all of the biphasic experiments, the organic and aqueous phases were separated and aliquots were withdrawn for quantitative analysis of glucose, fructose and HMF by HPLC. All the samples were filtered through a 0.2µm nylon filter (Cobert Assoc.) and pH re-adjusted to 6-7 by addition of aqueous NaOH solution prior to HPLC analysis. HPLC analysis was performed using a Waters 1525 HPLC system equipped with a 2998 PDA UV detector (280 nm) and a 2414 refractive index detector maintained at 333 K. The aqueous phase samples were analyzed using a PL Hi-Plex H-form carbohydrate column at 353 K with 5 mM H$_2$SO$_4$ as the mobile phase at a flow rate of 0.6 ml min$^{-1}$. The organic phase samples were analyzed using a Zorbax SB-C18 reverse phase column (Agilent) at 308 K, with a methanol:water (8:2 v/v) mixed solvent at a flow rate of 0.7 ml min$^{-1}$. Glucose or fructose disappearance was monitored using the refractive index detector, and the HMF production was monitored using the UV detector (280 nm). The definitions being used in the results and discussion section include: the conversion of glucose defined as the moles of glucose reacted divided by the moles of initial glucose, the selectivity of HMF defined as the moles of HMF produced divided by the moles of glucose reacted, and the yield of HMF defined as the glucose conversion multiplied by the HMF selectivity.
4.4. Results and Discussion

4.4.1 Effect of pH on the Activities of Different Lewis Acidic Metal Chloride Salts

In the aqueous media, the reactant, 0.3 M of glucose, together with the catalyst, 5mM of AlCl₃, was used under different solution pH values ranging from 2.5 to 5.5. Saturated levels of NaCl (33% by weight) were employed to facilitate the partitioning of HMF produced to the organic phase, which was 2-sec-butyl phenol (SBP). It has been shown in previous reports⁸², ²²¹ that SBP is very effective in extracting the furans made from carbohydrate dehydration in the reactive aqueous phase without concomitant absorption of hydrochloric acid. Practically, it is desirable to limit chloride ions in the organic phase because they can be detrimental for the catalysts used in the subsequent reactions.²¹² For the current work, highly selective portioning of the reaction product and catalyst were useful to improve analysis for the kinetic studies. A biphasic system was used as it has been shown recently that if the reaction is carried out in a monophasic system, in-situ formed acids during the hexose dehydration to HMF, particularly rehydration products of HMF-levulinic and formic acids, can self-catalyze the dehydration reaction.⁶¹ Extracting the produced HMF into the organic phase helped to diminish this concern. Similarly, glucose dehydration with 25mM YbCl₃ under different pH conditions was also performed. Several research groups have reported MCl₃-type metal salts as effective catalysts for glucose or xylose dehydration to produce high yields of furans in a biphasic system.⁷³, ⁸¹-⁸³, ⁸⁵, ²²² In these catalyst systems, the hypothesized scheme involves Lewis acids catalyzing the isomerization of the aldose to a ketose. Thus,
the combination of Lewis and Brønsted acidity could produce HMF selectively since the fructose dehydration is Brønsted acid-catalyzed and is more selective for HMF formation. The postulated reaction pathway is shown in Scheme 1.

Shown in Figure 1a is the time evolution of glucose conversion catalyzed by AlCl₃ in the biphasic batch reaction system. After the addition of 5mM AlCl₃ into nanopure water, the solution pH dropped to about 3.3, requiring the addition of either HCl or NaOH to adjust to the desired pH values. As seen in Figure 1a the rate of glucose conversion was highly dependent on the solution pH, with a lower rate found for higher pH values. The glucose conversion rates were similar for pH values of 2.5 and 3.5, but when the solution pH was raised to 5.5, a significantly lower rate of glucose conversion was observed. As similar reaction rates were found at pH values of 2.5 and 3.5, it could be hypothesized that the Lewis acidity was rate limiting rather than the Brønsted acidity since the proton concentration was 10 times higher at 2.5 than that of 3.5. The difference in glucose conversion rates as the pH increased could be related to the Al cation speciation under different pH conditions and will be discussed below.

In order to deconvolute the effect of intrinsic Brønsted acidity induced by the hydrolysis properties of the Al cation, the Yb cation was also investigated as a catalyst for glucose conversion under different pH conditions. In Figure 1b, the glucose conversion results using YbCl₃ as the catalyst for different solution pH values are shown. In sharp contrast to AlCl₃, relatively similar glucose conversion rates were observed independent of the pH conditions. Shown in Figure 2 is a comparison of the glucose
disappearance rates for both AlCl$_3$ and YbCl$_3$, clearly revealing an interplay between Lewis and Brønsted acids in the reaction system.

The cation speciation with the most Lewis acidic character of the species generated in the presence of water are the aqua ions, which are primarily present when the aqueous solution pH value is below the pK$_a$ hydrolysis constant value for the metal salt.$^{207}$ NMR studies with AlCl$_3$ have shown that the prevalent species present for aqueous solutions when the solution pH is less than 3 is the Al(H$_2$O)$_6^{+3}$ species.$^{206,223}$ When the solution pH is increased, the hydrolysis reaction occurs as shown by Equation 1.

\[
xM^{3+} + yH_2O \rightleftharpoons M_x(\text{OH})_{y(3x-y)}^{+(3x-y)} + yH^+ \quad \text{(Equation 1)}
\]

Therefore, when AlCl$_3$ was in contact with water, hydrolysis occurred resulting in both Lewis and Brønsted acidity so that the cationic species of AlCl$_3$ could catalyze glucose isomerization to fructose with subsequent dehydration of the fructose the protons (hydronium ions) as the catalyst. Lopez-Gonzalez et al.$^{224}$ have reported the effect of chloride ions on the thermodynamic equilibrium of trivalent cation hydrolysis. They found that in the presence of high concentration of chloride ion, significant amounts of MCl$_2^{+}$ were formed in an aqueous media, which was in agreement with recent studies by Choudhary et al.$^{215}$ Previous reports have shown that Al$^{+3}$ and Ln$^{+3}$ Lewis acid metal centers can coordinate simultaneously to carbonyl and alcohol groups to catalyze a hydride transfer from the alcohol to the carbonyl via a MPV reduction mechanism. The Lewis acid catalyzed isomerization of sugars in water has been demonstrated to proceed
by intramolecular hydride shifts very similar to that observed in MPV reductions. Under low pH conditions, AlCl$_3$ speciation in aqueous media is composed of primarily Al$^{+3}$, AlCl$^{-2}$, and Al(OH)$^{+2}$, which are active Lewis species for the glucose-to-fructose isomerization and thus similar glucose disappearance rates were observed at pH values of 2.5 and 3.5. However, at higher pH conditions, the equilibrium would shift towards the hydrolyzed cation, resulting in the less reactive complexed polycation species. Accordingly, a lower reaction rate was found at a pH of 5.5. In contrast, lanthanide metal salts have been demonstrated as water-compatible Lewis acids; so they will exist as Lewis acidic aqua ion species at higher pH values due to their higher pK$_a$ values of between 7.6 and 8.5. Indeed, as shown in Figure 1b, the rates of glucose disappearance were found to be relatively insensitive to pH when using YbCl$_3$ as the catalyst.

4.4.2 Activation Energies for Different Lewis Acid Metal Chlorides

As found in the pH studies, Lewis acidity appeared to play a more important role in affecting the glucose conversion rates than did the Brønsted acidity suggesting glucose/fructose isomerization as the rate limiting step. Activation energies studies for glucose conversion using different Lewis acids can provide more information about the interaction between the catalyst and the reactant. Although some kinetic analyses have been reported for single specific Lewis acid metal salts (e.g. chromium or aluminum) with carbohydrates, systemic studies compiling Lewis acidic cations from the same group but with different strengths have not been reported. Therefore, two different
groups of Lewis acids were chosen to be studied: the water-sensitive \( \text{AlCl}_3 \), \( \text{InCl}_3 \), and \( \text{GaCl}_3 \) group and the water-compatible \( \text{YbCl}_3 \), \( \text{DyCl}_3 \), and \( \text{LaCl}_3 \) group. Reaction temperatures of 150°C, 160°C and 170°C were chosen since this represented the common temperature range examined in Lewis acid catalyzed glucose dehydration studies. For glucose, reaction rates at temperatures below 150°C are rather difficult to determine due to the low rates and the possible convolution of the kinetic profile with the formation of organic acids during the reaction. The reaction-generated acids can self-catalyze the reaction and lead to perturbed rates. While at higher temperatures, the Lewis acid catalyzed glucose conversion is very fast and rates become difficult to quantify due to sampling challenges. In general, comparing the activation energies of Lewis acids in the same group is a more reliable way for understanding the effect of the intrinsic Lewis acidity of different metals on reaction of interest.

Shown in Table 1 are the glucose conversion rates measured for the different Lewis acids at a pH of 2.5 and reaction temperatures of 150-170°C. Across all of the reaction temperatures the rates followed the order of \( \text{LaCl}_3 < \text{DyCl}_3 < \text{YbCl}_3 \) for the water-compatible salts and \( \text{InCl}_3 < \text{GaCl}_3 < \text{AlCl}_3 \) for the water sensitive salts. Given these trends it was useful to determine if there was a correlation to their physicochemical properties such as Lewis acid/base hardness, ionic radius and the ease of reactant (glucose in this case) substitution for the coordinated water molecules around the hydrated cations. Both the lanthanum and aluminum series of chloride salts were chosen for this study due to their hard character and strong affinity towards the carbonyl oxygen or hydroxyl groups which are present in the glucose molecule. For example, amongst
In$^{3+}$, Ga$^{3+}$ and Al$^{3+}$, aluminum is the hardest Lewis acid and as a result, it should interact most strongly with the Lewis base-oxygen atoms in glucose, which was consistent the highest activity for the aluminum catalyst. As shown in Figure 3a and b, the ionic radius of the Lewis acid metal cations studied could be related to their reactivity for glucose conversion. For example, as the ionic radii decreased from In$^{3+}$, Ga$^{3+}$, to Al$^{3+}$, the turnover rate in the reaction based on the molar amount of each cation at 150°C increased from $33 \times 10^{-3}$ min$^{-1}$ for In$^{3+}$ to $316 \times 10^{-3}$ min$^{-1}$ for Al$^{3+}$. The same reactivity trend with ionic radii was also observed for the lanthanide series, with increasing turnover number in the following order: La$^{3+} < $ Dy$^{3+} < $ Yb$^{3+}$. For the metals within the same group, it could be hypothesized that the increased catalytic activity with decreasing ionic radius of the Lewis acid was due to stronger electrostatic attraction between the glucose molecule and the smaller cations, owing to their higher effective surface charge density. While relying on the ionic radius and the consequent effective surface charge density alone could explain the reactivity differences amongst the same studied group, a discrepancy arises when rates were compared between metal salts from different group. For example, the In$^{3+}$ radius (94pm) is smaller than that for Yb$^{3+}$ (101pm), but the relative reactivity was reversed, with Yb$^{3+}$ being the more active catalyst at all of the temperatures studied. A possible reason for this observation could be that the exchange rate constants for substitution of inner-sphere water ligands, or water exchange rate constant (WERC) by an incoming substrate (glucose under this circumstance) have also been suggested to play a role in controlling the Lewis acidity of metal ions in an aqueous media. As a result, the facile ligand exchange between a water ligand and the glucose substrate for ytterbium
compared to indium could lead to a higher glucose conversion rate. While there have been limited studies on this effect, Ishida et al. performed NMR experiments to study the interaction between La$^{3+}$ and glucose, and no spectra changes were observed at least at room temperature.\textsuperscript{228}

From the temperature studies activation energies (Ea) were estimated for all of the metal salts. First order kinetics relative to the sugar concentration have been widely assumed in the kinetic analysis of Brønsted acid catalyzed conversion of monosaccharides.\textsuperscript{8, 62, 229} Apparent activation energies were calculated using the initial rate of glucose disappearance and the Arrhenius relationship (Equation 2), assuming a first order reaction rate expression based on glucose.

$$k = A \times \exp \left( \frac{-E_a}{RT} \right)$$

(Equation 2)

Table 1 shows the apparent activation energies for all the Lewis acids studied. The Ea values were found to be 125±3 kJ/mol, 93±3 kJ/mol, and 128±18 kJ/mol for AlCl$_3$, InCl$_3$, and GaCl$_3$, respectively. These values were essentially in the range of the ~129 kJ/mol reported for a similar catalyst, CrCl$_3$, by Choudhary et al.\textsuperscript{86} The apparent activation energies for glucose conversion with these Lewis acids was slightly lower than the commonly reported values (between 130 kJ/mol and 140 kJ/mol) for strong mineral acids.\textsuperscript{8} No direct link between the apparent energy values and the reaction rate constants of the three different Lewis acids was observed, suggesting that other factors such as exchange rate constants for substitution of inner-sphere water ligands may also partially
determine the rate of glucose conversion by affecting the pre-exponential factor in the reaction rate equation. The apparent activation energies determined for the lanthanum chlorides were 87±3 kJ/mol, 121±2 kJ/mol, and 169±10 kJ/mol for YbCl$_3$, DyCl$_3$, and LaCl$_3$, respectively. The Ea values of these Lewis acids were also found to be lower than typical values for Brønsted acid-catalyzed glucose conversions with the least active, LaCl$_3$, as an exception. Interestingly, the larger apparent activation barriers for these salts did correlate with slower reaction rates. In summary, the apparent activation energies for the Lewis acid salts studied in this work were generally found to be lower than the reported Ea values associated with Brønsted acids.

4.4.3 Kinetic Analysis with Fructose

As shown in Scheme 1, glucose dehydration reactions mediated by Lewis acids have been proposed to proceed in a two-step sequence, with a reversible and relatively slow aldose-to-ketose isomerization catalyzed by the Lewis acid catalyst and a fast fructose dehydration to form HMF catalyzed by the Brønsted acid. We previously reported that LnCl$_3$ could readily catalyze the glucose to HMF conversion with moderate yields even under high pH conditions, such as a pH value of 5.5. Therefore, experiments were performed to examine whether Lewis acids could play a role in the generally accepted Brønsted acids-catalyzed fructose dehydration reaction.

As can be seen in Figure 4, the results of fructose conversion using AlCl$_3$, YbCl$_3$ or no Lewis acid catalyst all at the same pH value of 2.5 were different. The rates of fructose conversion were calculated to be 32.6±0.4 µmol/min, 21.9±0.2 µmol/min, and
11.2±1.1 µmol/min for AlCl$_3$, YbCl$_3$ and HCl alone, respectively. Since the pH values were the same it would appear that the difference conversion rates were attributed to some contribution from the Lewis acidity. Figure 5 summarizes the HMF selectivities from fructose for the three different catalyst systems. Of note was that when the fructose conversion was around 60%, the HMF selectivity using AlCl$_3$ or YbCl$_3$ was about 60 mol%, whereas when using HCl alone the selectivity was about 70 mol%. The difference in HMF selectivity suggested that while Lewis acids accelerated the rates of fructose disappearance they seemed to also catalyze undesired side reactions such as the formation of humic molecules or rehydration of HMF to other acids. As the Lewis acid appeared to lower HMF selectivity in fructose dehydration while enhancing glucose to fructose isomerization, an appropriate Lewis to Brønsted acidity ratio would be required to optimize HMF yields. Similar observations were also reported by Weingarten et. al.,$^{230}$ where the authors found that an appropriate ratio between the Lewis and Brønsted acidity of solid acids was very important to maximize the yield of furfural from xylose. In that work, an increase in the number of Lewis acid sites decreased furfural selectivities by catalyzing the side reaction leading to humin formation. Shown in the supplemental Figure S1 is the time evolution of fructose conversion using AlCl$_3$ and HCl alone as a catalyst. It was observed in the case of AlCl$_3$ that glucose was also formed, though in low abundance. In contrast, no glucose was observed when only HCl was used. This observation further confirmed the reversible isomerization between glucose and fructose as postulated in Scheme 1.
4.4.4 Effect of Lewis Acid Metal Salts Concentration on Glucose Conversion Kinetics

Glucose conversion was also investigated at catalyst concentrations ranging from 2.5mM to 10mM and 25mM to 100mM for AlCl₃ and YbCl₃, respectively. As reference, the 5wt% glucose solution used in the current work corresponded to a concentration of 0.3M, which was greater than any catalyst concentration studied. Shown in Figure 6 is the initial rate of glucose disappearance measured at each of the different catalyst concentrations when AlCl₃ was used as the catalyst. As can be seen in the figure, the initial rate increased with the catalyst concentration. When the concentration of AlCl₃ increased from 2.5mM to 5mM, the initial rate of glucose disappearance increased from 4.9 µmol/min to 7.4 µmol/min, which was less than the value of approximately 9.8 µmol/min that would be expected if the reaction was first-order in the catalyst concentration. A similar trend was also found when YbCl₃ was used as the catalyst (see Figure S2). Scheme 1 and the kinetic analysis in the previous section suggested that the Lewis acid-catalyzed glucose/fructose isomerization reaction was the rate-limiting step in the proposed reaction pathway. However, all of the results taken together suggested that the glucose conversion reaction was not first-order in MCl₃ concentration.

This observation was consistent with that recently reported by Choudhary and co-workers using CrCl₃ as the catalyst. The authors performed computational analysis to demonstrate that the CrCl₃ speciation in the reaction system depended on the concentration of CrCl₃, pH values, etc. When CrCl₃ was dissolved in an aqueous media containing HCl, a distribution of products including, Cr³⁺, CrCl²⁺, and CrOH²⁺, was
found. Further, the study showed that the initial glucose conversion rate did not increase linearly with Cr$^{3+}$ and CrCl$^{2+}$ concentration and as a result, the system was not first order in the amount of CrCl$_3$ added. In our study, a high chloride (Cl$^-$) concentration was used and as such it would be expected that significant amounts of Al$^{3+}$ and AlCl$^{2+}$ or Yb$^{3+}$ and YbCl$^{2+}$ were present in the solution. Thus speciation of the catalyst could be responsible for the results observed in our catalyst concentration study.

4.4.5 Kinetic Isotope Effects (KIEs)

The MCl$_3$-catalyzed glucose conversion reactions in this manuscript produced fructose and a significantly smaller amount of mannose. These two sugars accounted for all the carbohydrate products detected in the solution. Fructose is the isomer of glucose in which a carbonyl group is at the C2 position and mannose is the C2 epimer of glucose. The product distribution after contacting glucose with MCl$_3$ indicated that the glucose most likely to interacted with the Lewis acids at the C1 and C2 position. In work with heterogeneous Lewis acids, Davis and coworker used $^{1}$H and $^{13}$C NMR spectroscopy techniques to demonstrate that their Sn-beta zeoltie catalyzed glucose/fructose isomerization via the MPV reduction mechanism. They proposed an intra-molecular hydride transfer from the C2 to C1 position with the Lewis acid center acting as a metalloenzyme-like catalyst. We and other research groups have reported glucose dehydration to form HMF catalyzed by MCl$_3$-type catalytic systems in which a similar MPV reduction mechanism was proposed as being responsible for the transformation based on the intermediate formation involving both fructose and mannose.
experiments with glucose deuterated at the C2 position were performed and their reaction kinetics were analyzed to provide further validate this postulate for the homogeneous MCl$_3$ Lewis acids.

Scheme 2 provides a proposed reaction mechanism using homogeneous MCl$_3$ Lewis acids. In this reaction pathway, the proton at the C2 position would migrate from the C2 to C1 position according to the MPV reduction and this intra-molecular hydride shift should be kinetically-relevant. Shown in Figure 7 are glucose conversion kinetics using AlCl$_3$ as the catalyst with glucose either labeled at the C2 position or unlabeled in which all other reaction conditions were held constant. A significant kinetic isotope effect (KIE) was found with $k_H/k_D=1.34$, which confirmed that the proton at the C2 position was involved in the rate-limiting step, which was in agreement with the proposed reaction mechanism.

4.5. Conclusions

In summary, using homogeneous Lewis acid metal salts to catalyze glucose conversion particularly in aqueous media is of great importance to develop a basic scientific understanding and potentially help the deployment of practical applications. Unfortunately, there are apparently isolated results presented in the literature, as the comparison between different Lewis acid catalysts is not performed in a systematic manner in which the effect of Lewis and Brønsted acidity on the glucose conversion was deconvaluted. Different Lewis acids for glucose conversion at various pH conditions were studied in this manuscript and it has been found that, depending on the hydrolysis
properties of each Lewis acid, H⁺ concentration was responsible for controlling the Lewis acidity of MCl₃-type catalyst. Estimated activation energies using different Lewis acid metals salts were found to be considerably lower than those of their Brønsted acid counterparts, indicating different reaction mechanisms can be accountable for these two catalytic systems.

Further experiments using fructose as feedstock demonstrated that Lewis acids could also affect dehydration reaction of fructose, which was traditionally thought to be Brønsted acid catalyzed. While the use of Lewis acids can accelerate the glucose/fructose isomerization reaction, data shown in this report also clearly reveal that Lewis acids can lead to lower HMF selectivity for fructose dehydration. In order to maximize the HMF yield starting from glucose, an appropriate amount of Lewis and Brønsted acids should be optimized.

The effect of catalyst concentration on initial glucose conversion rates was also studied. The results indicated that initial glucose conversion rate was not first-order to MCl₃-type Lewis acid catalysts. Computational work by other researchers has suggested the MCl₃ speciation in water depended on MCl₃ concentration, and as a result the reaction rate was calculated to not be first-order to the catalyst. Glucose deuterated at the C2 position was used to provide further insight about the reaction mechanism. Considerable KIE of 1.33 was found based on the reaction kinetic profile, in agreement with the MPV reduction mechanism proposed in reaction Scheme 2.
Acknowledgements

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Reference


Schemes, Figures and Tables

Scheme 1. Glucose dehydration to HMF reaction pathway for combined Lewis and Brønsted acid catalysts.
Figure 1A. Results of glucose conversion using AlCl$_3$ as a catalyst under different pH conditions.$^{[a]}$ Reactions were run using 5mM AlCl$_3$ as a catalyst under the indicated pH conditions and water containing 5 wt% glucose (saturated with 33% NaCl). SBP was used as organic extracting solvent and an organic to aqueous mass ratio of 2 was used. Reaction temperature at 443K.
Figure 1B. Results of glucose conversion using YbCl$_3$ as a catalyst under different pH conditions.$^{[a]}$

![Graph showing conversion vs time with different pH conditions]($\text{Conversion (mol %)}$ vs $\text{Time (min)}$)

$^{[a]}$ Reactions were run using 25mM YbCl$_3$ as a catalyst under the indicated pH conditions and water containing 5 wt% glucose (saturated with 33% NaCl). SBP was used as organic extracting solvent and an organic to aqueous mass ratio of 2 was used. Reaction temperature at 443K.
Figure 2. Reaction rate of glucose conversion with and under different pH values.
Table 1. Reaction rates and estimated activation energies of different MCl$_3$ catalysts$^{[a]}$

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<th>T, °C</th>
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$^{[a]}$ Reactions were run using 25mM MCl$_3$ as a catalyst under pH of 2.5 and water containing 5 wt% glucose (saturated with 33% NaCl). SBP was used as organic extracting solvent and an organic to aqueous mass ratio of 2 was used. Reaction temperatures were as indicated. $^{[b]}$ 5mM AlCl$_3$ was used to determine the initial rates because of the high activity using AlCl$_3$. 


Figure 3A. Correlation of turnover number with ionic radii of Lewis acid salts (aluminum group) [a]

[a] Reactions were run using 25mM MCl$_3$ as a catalyst under pH of 2.5 and water containing 5 wt% glucose (saturated with 33% NaCl). Ionic radius is based on 6-coordinated cation. Turnover number was based on the mols of Lewis acid present in the solution.
Figure 3B. Correlation of turnover number with ionic radii of Lewis acid salts (lanthanum group) [a]

[a] Reactions were run using 25mM LnCl$_3$ as a catalyst under pH of 2.5 and water containing 5 wt% glucose (saturated with 33% NaCl). Ionic radius is based on 6-coordinated cation. Turnover number was based on the mols of Lewis acid present in the solution.
Figure 4. Correlation of rate constants (k) with ionic radii of Lewis acid salts (lanthanum group) [a]

[a] Reactions were run using 25mM YbCl$_3$, 5mM AlCl$_3$ or no Lewis acid at a pH of 2.5 conditions and water containing 5 wt% glucose (saturated with 33% NaCl). SBP was used as organic extracting solvent and organic to aqueous mass ratio of 2 was used. Reaction temperature at 433K.
Figure 5. Fructose conversion and HMF selectivity using different catalysts.
Figure 6. Initial rate of glucose conversion using AlCl$_3$ at different concentrations$^a$.

$^a$ Reactions were run using 2.5, 5, 10mM AlCl$_3$ at a pH of 2.5 and water containing 5 wt% glucose (saturated with 33% NaCl). SBP was used as organic extracting solvent and organic to aqueous mass ratio of 2 was used. Reaction temperature at 433K.
Scheme 2. Proposed glucose dehydration to HMF reaction pathway by a combined Lewis and Brønsted acid catalysts.\[a\]

[a] M represents Lewis acid metal center and 6-coordination configuration of the cation was used to illustrate the plausible mechanism.
Figure 7. Correlation of rate constants (k) with ionic radii of Lewis acid salts (lanthanum group) [a]

[a] Reactions were run using 25mM AlCl$_3$ at pH of 2.5 and water containing 5 wt% unlabeled glucose or deuterated glucose at C-2 position (saturated with 33% NaCl). SBP was used as organic extracting solvent and organic to aqueous mass ratio of 2 was used. Reaction temperature at 443K.
CHAPTER 5. PYROLYZING RENEWABLE SUGAR AND TAURINE ON THE SURFACE OF CARBON NANOTUBE (CNT) AS HETEROGENEOUS CATALYSTS FOR HYDROXYMETHYLFURFURAL (HMF) PRODUCTION

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5.1. Abstract

Conversion of biorenewable feedstocks into transportation fuels or chemicals likely necessitates the development of novel heterogeneous catalysts with good hydrothermal
stability due to the nature of highly oxygenated biomass compounds and the prevalence of using water as processing solvent. Using renewable feedstock such as sugars as catalyst precursor complementally realizes the goal of green chemistry. In this work, a robust and sustainable catalyst preparation method pyrolyzing glucose and taurine in the presence of CNT to obtain a versatile solid acids has been demonstrated. Characterization and textual properties of the catalysts were probed through the utilization of TEM, SEM, TGA, XPS. Additionally, solid state nuclear magnetic resonance(ssNMR) spectroscopy has been exploited to further elucidate the chemical nature of carbon species deposited on the surface of CNT. Al(OTf)$_3$ as a model Lewis acidic metal salt was successfully supported on sulfonic groups tethered CNTs and tested for C$_6$ sugar dehydration for the production of HMF in tetrahydrofuran(THF)/water solvent system with good recyclability.

5.2. Introduction

Due to the rapidly growing world energy and materials consumption with diminishing petroleum reserves, economical and environmental concerns have risen, urging the utilization of renewable sources of carbon for liquid transportation fuels and chemicals. Biomass is uniquely situated to provide an alternative to petroleum sourced carbon because of its abundance and sustainability$^{11}$. However, in contrast to traditional feedstocks, molecules derived from the carbohydrate fractions of biomass consist of highly oxygenated compounds of which functionality must be removed instead of being added so as to replace the highly reduced carbon platform molecules typical of the modern fuel and chemical industry.$^{231}$ Therefore, processing of these materials will
greatly differ from what has been well researched and employed in the petrochemical industry. The need to adapt to these new feedstocks and processing conditions are particularly challenging for the field of heterogeneous catalysis.\textsuperscript{187} It is important that the heterogeneous catalysis community perform research with common biorenewable compounds in order to gain understanding and subsequent controlling of the active site environment as well as develop catalysts with hydrothermal stability.\textsuperscript{187}

Common catalysts employed in the petroleum industry such as zeolites have been shown to be not stable with exposure to hot water and stability must be considered for biomass upgrading.\textsuperscript{232} Consequently, hydrothermal stability concerns have promoted recent research into carbon-based supports for biorenewable applications.\textsuperscript{233, 234} One particular carbon catalyst support receiving a significant amount of attention in recent years are carbon nanotubes.\textsuperscript{234, 235} Carbon nanotubes (CNTs) are an interesting material to use to gain an understanding of biorenewable relevant reactions for reasons other than their hydrothermal stability. For instance, they offer uniform and turnable textual properties such as porosity that can be easily manipulated, allowing for greater control over the catalyst active site. CNTs also have a relatively high surface area and relatively less microporosity making it less likely to encounter mass transport limitations when it is used as catalyst supports.\textsuperscript{236}

Considering the difficulty in changing an infrastructure built around current petroleum derived fuels and chemicals, it would be desirable to produce bio-derived products that can either directly replace petroleum-based chemicals, or serve as functional replacements. One example that has attracted increasing interest is the
development of biorenewable plastics derived from carbohydrate portion of the lignocellulosic biomass. Among all the proposed platform chemicals that can be converted to monomers for subsequent production of polymers, 5-hydroxymethylfurfural (HMF) has been identified as a promising platform chemical candidate, which can be used to produce polyethylene furanics (PEF) to replace petroleum based PET.

HMF has been mainly produced from C₆ monosaccharide, glucose or fructose, using acid catalysts. In the past decade, various catalysts such as homogeneous sulfonic acid, heteropolyacids (HPAs), heterogeneous metal-oxide based catalysts like tin-Beta zeolites, Nb₂O₅ have all been reported to catalyze the dehydration reaction. Very recently, a class of metal salts such as AlCl₃, SnCl₄, GeCl₄, YbCl₃ dissolved in either aqueous or ionic liquid media, have been investigated as extremely effective catalysts for HMF production. The unique catalytic performance of these metal salts catalytic systems have been attributed to the combined of Lewis and Bronsted nature of metal cations and hence facile interaction with sugar molecules to promote HMF synthesis. Although promising, recycling and separation of the homogeneous metal salts may raise concerns on the practicability of such systems. In order to solve this dilemma, it can be advantageous to immobilize these metal salts on a solid support.

In this contribution, we report the development of hydrothermally stable novel catalyst systems able to perform relevant biorenewable reactions be developed. For this purpose, Lewis acid catalysts immobilized on CNT appear to promising with the potential to perform solvent-mediated carbohydrate conversion. In this work, Al(OTf)₃
was chosen as the model Lewis acid metal salt which has been shown in previous work to be an effective homogeneous catalysts for dehydration of sugars.\textsuperscript{81} Co-pyrolysis of glucose and taurine with CNT under controlled experimental conditions (200°C and 250°C) resulted in a hybrid material where sulfonic groups were tethered to the surface of CNT. Solid-state NMR were used to determine the chemical structure and bonding nature using $^{13}$C labeled glucose and $^{13}$C or $^{15}$N labeled taurine. The electrostatic interaction between sulfonate and aluminum cation was exploited for the immobilization of the Lewis acid catalyst. Lewis acid immobilized CNT catalysts were subsequently tested for their activities for glucose and fructose dehydration reaction, as shown in Scheme 1. In addition, catalyst recyclability studies using fructose were also carried out and Al leaching test with ICP analysis was also performed after each run to study the stability of the catalyst.

5.3. Experimental

5.3.1 Catalyst Synthesis

Before experiment, carbon nanotube was ultrasonicated with Branson Digital Sonifier\textsuperscript{®} for 15min with 90% power output to remove amorphous carbon and introduce oxygenated groups to the surface. To synthesize sulfonate tethered CNT, an aqueous solution containing consisting of 0.71M glucose(Fisher), 0.355M taurine(Sigma-Aldrich) and 0.355M NaOH(Fisher) was mixed with CNT(combined weight glucose and taurine accounts for 15wt% carbon content relative to the weight of CNT). The mixture was then sonicated for 5min, followed by heating to 120°C with ramp rate of 1°C /min or 5°C/min and held for 3hr until dried. The pyrolysis was done at 200°C or 250°C under
200mL/min flowing N\textsubscript{2} protection with temperature ramping rate of either 1°C/min or 5°C/min and held at desired temperature for additional 10hr. The same protocol was repeated again to introduce adequate amount of functional groups. Table 1 summarized the synthesis condition for different materials.

To make the solid Lewis acid(3-16-L), the obtained sulfonate/CNT 0.8g was first immersed in 1M NaCl solution and stirred for 24 hr, followed by contacting with Al(OTf)\textsubscript{3} (Sigma-Aldrich, 1.0g) in ethanol under 80°C for 24hr. Solid Bronsted acid(3-16-B) was synthesized in a similar procedure with excess amount of 1.6M HCl aqueous solution to fully protonate the sulfonate group.

5.3.2 Materials Characterization

The catalysts were characterized using scanning electron microscopy (SEM), transmission electron microscopy (TEM), x-ray photoelectron spectroscopy (XPS), N\textsubscript{2} adsorption/desorption, and thermogravimetric analysis (TGA). TEM images were taken on a Tecnai G2 F20. XPS testing was performed on a Phi 5500 Multitechnique system using an Al K\alpha x-ray source. A C1s location of 284.6 was used for peak corrections. TGA experiments were done on a Perkin-Elmer STD 600 under the flow of 50 ml/min air and a temperature ramp of 10 °C/min from 50-900 °C. N\textsubscript{2} adsorption/desorption testing occurred on a Micromeritics ASAP 2020 with the BET method used for surface area calculations.

5.3.3 Solid-state NMR

Solid-state magic-angle-spinning NMR studies were carried out on a Bruker Avance 400 9.4 T spectrometer. A 4-mm hybrid probehead and a 2.5-mm triple-resonance
probehead were used; unless otherwise stated, all experiments used the 4-mm hybrid probehead.

$^{13}$C was observed at 100 MHz. The $^{13}$C pulse lengths used were: 4 μs for the experiments using “4-16-1”, “UGT250” and “GUT250”; 4.4 μs for “4-22 CNT2”; uniformly $^{13}$C-labeled glucose was obtained from Cambridge Isotope Laboratories. DP buildup curves were created by performing a series of DP/echo experiments on samples “4-16-1” (recycle delay up to 40 s) and “UGT250” (recycle delay up to 45 s), in order to measure the spin-lattice relaxation rate for each. This relaxation rate is given by the parameter $T_1$ and determines the recycle delay required for the other experiments. DP/gade/echo experiments were conducted on both samples to investigate the amount of non-protonated $^{13}$C in each.

Uniformly $^{13}$C-labeled taurine was obtained from Cambridge Isotope Laboratories. A DP/echo experiment was performed on the sample “4-22 CNT2” to determine the structural environment in the post-reaction structure of the carbons originating from taurine. A DP/gade/echo experiment was used to investigate the amount of non-protonated $^{13}$C in the sample. Using the 2.5-mm triple-resonance probehead, multiCP and multiCP/gade experiments were performed on “4-22 CNT2”, “4-30-1”, and “4-30-2”. These experiments were used for the same purposes described above for the DP/echo and DP/gade/echo experiments.

The $^{15}$N pulse length was 11 μs and the recycle delay was 1 s for the experiment using “4-22 CNT1”. The $^{15}$N pulse length was 10.2 μs and the recycle delay was 4 s for the experiment using “NUGTCNT250”. $^{15}$N-labeled taurine was obtained from
Cambridge Isotope Laboratories. A multiCP experiment was used to quantify the forms of nitrogen present in the samples labeled with both $^{15}$N-taurine and $^{13}$C-glucose. A multiCP/gade experiment was used to measure the amount of non-protonated $^{15}$N in these samples.

5.3.4 Reaction Testing

Glucose and fructose were tested as model carbohydrate molecules for HMF production with the prepared CNT-based catalysts in 10mL thick-walled glass reactor(Alltech). In a typical experiment, 2.0 g different organic solvent containing 2wt% of glucose or fructose with different solid catalysts was added to the Alltech reactor and a triangular stir bar (Fisher Scientific) was also added to allow for adequate agitation. The reactor was then sealed with PTFE liner covered caps (Fisher Scientific) and immersed in the oil bath at desired temperatures and stirred at 400 rpm. Catalyst recyclability test was performed with fructose being the substrate in the THF/water solvent system. After each run, the organic solvent was decanted and the catalyst was kept and dried before fresh solvent containing fructose was added again to run the reaction. In order to test the possible Al catalyst leaching, after each reaction, the supernatant of abovementioned fructose reaction was sampled and prepared for ICP analysis.

Sample analysis was performed using a Waters 1525 HPLC system equipped with a 2998 PDA UV detector at 280 nm and a 2414 refractive index (RI) detector maintained at 333 K. The aqueous phase samples were analyzed using a PL Hi-Plex H-form carbohydrate column at 353 K with 5 mM H$_2$SO$_4$ at a flow rate of 0.6 ml min$^{-1}$ as the mobile phase. The organic phase samples were analyzed using a Zorbax SB-C18 reverse
phase column (Agilent) at 308 K, with a methanol: 5 mM H$_2$SO$_4$ (8:2 v/v) binary solvent as the mobile phase at a flow rate of 0.7 ml min$^{-1}$. The conversion/selectivity being used in this manuscript are defined as below: the conversion of glucose defined as the moles of glucose reacted divided by the moles of initial glucose, the selectivity of HMF defined as the moles of HMF produced divided by the moles of glucose reacted, and the yield of HMF defined as the glucose conversion multiplied by the HMF selectivity.

5.3.5 Inductively Coupled Plasma Mass Spectrometer (ICP-MS) Analysis of Al Leaching

The aluminum content in each sample was analyzed by inductively coupled plasma mass spectrometer (ICP-MS) (Bruker Aurora Elite). The instrument parameters (Table 1) were optimized for maximum sensitivity with low levels of metal oxide (CeO$^+/Ce^+ \leq 2\%$) and doubly charged (Ba$^{2+}$/Ba$^+$ $\leq 3\%$) ions. Calibration standards were prepared by serial dilutions of a commercially available aluminum ICP-MS standard (SPEX CertiPrep) with 5% aqueous hydrochloric acid (HCl). The samples were also prepared to have a matrix of 5% aqueous HCl. The solid CNT catalyst samples (~5 mg) were dissolved in concentrated HCl and then diluted with deionized water to a final HCl concentration of 5% (final mass of approximately 10 g). The original reaction supernatant samples were diluted 50 to 100 fold with 5% aqueous HCl.

5.4. Results and Discussion

5.4.1 Catalyst Characterizations

Sulfonic acid groups were introduced to the surface of CNT by co-pyrolyzing glucose and taurine. Before pyrolysis, the parent CNT has a BET surface area of 304 m$^2$/g and pore volume of 1.13 cm$^3$/g, which were reduced to 118 m$^2$/g and 0.33 cm$^3$/g.
respectively. This change in porosity properties provides an indirect evidence of the successful deposition of functional groups on the surface of CNT. TEM and EDS imaging studies have provide further confirmation of the successful synthesis of sulfonate tethered CNT catalysts. As shown in Figure 1, the representative solid Lewis acid catalysts (after the immobilization of Al(OTf)₃) revealed a typical morphology of multi-walled carbon nanotube, see Figure 1 a). EDS mapping revealed a homogeneous distribution of sulfur element, indicating the sulfonic groups are impregnated throughout the CNT surface. Further EDS data was summarized in Figure 2 for C, O, Al, S elements. By comparison, it can be concluded that both Al and S are well dispersed throughout CNT surface, proving the effectiveness of the pyrolysis and immobilization as catalyst preparation methods. Additionally, shown in Figure 1 c) and d) are the images of spent Lewis acid catalyst after being subjected to the reaction condition of 160°C in THF/water for 3hr. Although ICP analysis of supernatant would be a more definitive method to quantify the stability of immobilized Al catalyst, which will be discussed below, the visual TEM/EDS images demonstrated a similar morphology/S distribution of intact and spent Lewis acid catalysts.

5.4.2 Solid-state NMR

In all experiments, the signal from the MWCNT themselves is considered to be negligible.

Sample “4-16-1” loses less signal than “UGT250” in the DP/gade/echo experiment (Figure 3), indicating that fewer of the carbons contributed by glucose in the material are
protonated when the reaction is carried out with MWCNT. The sample “4-16-1” also exhibits a shorter $T_1$ than its counterpart with no MWCNT, “UGT250”. This indicates that including MWCNT in the synthesis causes more unpaired electrons to be present in the glucose-taurine material, since unpaired electrons are known to accelerate spin-lattice relaxation and shorten $T_1$.

In several similar materials, higher reaction temperature corresponded to a shorter $T_1$ as well as an increase in aromaticity of the glucose-taurine material. When $T_1$ decrease is used as a proxy for aromaticity increase, the new data indicate that “4-16-1” has a higher aromaticity than “UGT250”. By comparison to other control samples, it can be estimated that “4-16-1” is similar in aromaticity to a previously-prepared glucose-taurine material (without MWCNT) with a reaction temperature of 400C. Higher aromaticity is consistent with fewer of the aromatic carbons being protonated.

As the recoupling time in the DP/gare/echo experiment increases, $^{13}$C’s farther and farther from 1H’s are dephased (lose signal). Carbons closer to protons will dephase more quickly, so this can be a particularly useful tool for probing the size of aromatic domains. The aromatic carbons in “UGT250” are dephased more quickly than those in “4-16-1”, and all at about the same rate. The $^{13}$C’s in different environments within “4-16-1” dephase at different rates, and the carbonyl carbons dephase the slowest. This indicates that the carbonyl groups in “4-16-1” are farther from hydrogen atoms than in “UGT250” and that the aromatic domains in “4-16-1” are larger than those in “UGT250”.
Of all the $^{15}$N contributed by the labeled taurine in “4-22 CNT1”, 74% is retained in the sample provided. The sample “NUGT250” was used as a reference with known N content to determine this. Of the pyrollic $^{15}$N in “4-22 CNT1”, 66% is nonprotonated.

In the experiments on samples containing 13-C-labeled taurine using the 4-mm probehead (Fig. 4a), no indication was found of methylene groups. If the methylene groups were intact after reaction, they would have increased the DP/gare/echo dephasing rate beyond what was observed in “4-22 CNT2” and “GUT250”. In addition, no peaks associated with N-CH2 or S-CH2 bonds were detected from either sample in the DP/echo spectra.

Inefficient 1H decoupling could cause methylene peaks to be underrepresented, so the experiment on “4-22 CNT2” was repeated using the 2.5-mm probehead. A smaller rotor diameter is known to increase effective decoupling power. For the 2.5-mm probehead spectra, multiCP was used instead of DP. Again, in the “4-22-CNT2” quantitative spectrum (Fig. 4b), no sign of the original alkyl moiety from taurine remained.

Two variations of the material were prepared to examine the effect on reaction temperature and the rate of temperature increase on the final environment of the taurine methylene carbons. Both of these samples (“4-30-1” and “4-30-2”, respectively) were analyzed using multiCP and multiCP/gade with the 2.5-mm probehead. The spectra are shown for comparison with that of “4-22 CNT2” (Fig 4b).

The sample that was reacted at 250C but was ramped up to that temperature more slowly than in previous reactions, “4-30-2”, shows a similar distribution of intensity
between the aromatic and aliphatic regions of the spectrum. However, its multiCP spectrum shows a larger loss (more protonated carbons) in the aromatic region. A larger fraction of protonated carbon could indicate smaller aromatic domains, but a DP/gare experiment would be the best way to establish that. The sample reacted at 200°C (“4-30-1”) shows less intensity in the aromatic region and more intensity in the region associated with methylene groups than is found in either of the two samples reacted at 250°C. This demonstrates that a lower reaction temperature can increase the retention of the alkyl moiety of taurine in the final product, and that those carbons are in the range expected for N-CH2 and S-CH2 bonding. Since the intensity in this region is composed of overlapping peaks, the determination of the exact bonding environment of these methylene groups will require some modeling of potential structures. The predicted 13C and 15N NMR spectra based on those structures can be compared to the experimental results for the 13C-labeled and 15-N-labeled samples.

5.4.3 Reaction Testing

Initial reaction testing with different catalysts was performed in a binary solvent consisting of THF and DMSO, which is a well-known reaction solvent to minimize side reactions. As shown in supplemental Figure 2, the glucose/fructose conversion kinetics is highly dependent on the catalysts used. For example, in the glucose conversion plot, the reaction barely occurred in the absence of catalysts added. All the added catalyst combination can promote glucose conversion, as can be seen in the plot, with the improvement in the order of combination of solid Lewis and Bronsted acids–solid Lewis
acid-solids Bronsted acid, which is in agreement with our previous work. However, for all these reactions, low selectivity ranging from 0 to 20 mol% was obtained. This can be ascribed to undesired side reactions on the surface of CNT and likely be associated with metal cation catalysis to induce the formation of humins or so. Since solid Lewis acid was found to be quite active for the catalysis, a combination of Lewis and Bronsted acid were chosen to be used for later conversions. Unlike its glucose counterpart, catalytic performance of the solid catalysts for fructose was improved significantly. The conversion kinetics showed that under reaction temperature of 120°C, fructose conversion was completed within the first 3 hr with selectivity greater than 85 mol%.

Based on the initial reactivity/selectivity trends, we chose to use THF/water binary solvent system and a combination of solid Lewis and Bronsted acid catalysts for further reaction testing. Although DMSO can generally enhance sugar dehydration selectivity by minimizing side reactions, its practical implementation can be problematic due to its high boiling point and cost. Figure 5 summarized the reaction result of fructose conversion using reaction media of THF/water and reaction temperature of 160°C. Similar to the trend observed using THF/DMSO solvent, conversion rate using fructose as feedstock was faster than glucose. In addition, selectivity of HMF from fructose was about 60 mol% while less than 10 mol% selectivity from glucose was achieved.

Catalyst stability and recyclability under reaction condition are of great importance in industrial applications. Regarding this aspect, recyclability of the solid catalysts was carried out in fructose reaction. As shown in Figure 6, three consecutive reactions were run with fructose as feedstock following the procedure of 1) carefully discard the
supernatant 2) keep and wash the remaining solid using sugar-free THF/water solvent 3) add fresh solvent containing fructose to the next reaction. The reaction kinetic profile showed a relatively similar reaction rate between the three runs with little loss of catalyst activity. Additionally, selectivity towards HMF was also kept around 60mol%, which was slightly lower than THF/DMSO solvent system. Aside from the phenomenal reaction kinetics data, the supernatant after each reaction was also analyzed for possible Al leaching. The calculated Al leaching was found to be 3.3%, 2.2%, 1.8%, respectively.

5.5. Conclusions

In summary, the synthesis of sulfonic group tethered CNT solid catalysts has been successfully demonstrated. Solid-state NMR is a powerful tool to provide quantitative information about the chemical nature of surface carbon content. By manipulating synthesis conditions, the catalysts with desired acid density can be made and furthermore, the functionalized CNT can be used as catalyst support to immobilize homogeneous metal cation catalyst for various catalytic applications. The hybrid Al/CNT catalysts were tested in this work for both glucose and fructose dehydration to HMF and the catalyst stability and recyclability have been shown to be effective. Although promising, more study is required to design better ligand field on the surface of CNT to achieve higher selectivity and less catalyst leaching is the focus of future research directions.

References


Schemes, Figures and Tables

Scheme 1. Solid Lewis/Bronsted acid catalysts for HMF production from C₆ sugars
Table 1. Synthesis conditions of different materials.

<table>
<thead>
<tr>
<th>Sample Code</th>
<th>Isotopic Labeling</th>
<th>Heating conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-16-1</td>
<td>Uniform 13C: Glucose</td>
<td>Pyrolysis temperature of 250°C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ramp of 1°C from r.t. to 120°C, 10°C from 120°C to 250°C</td>
</tr>
<tr>
<td>4-22 CNT1</td>
<td>Uniform 13C: glucose, Uniform 15N: taurine</td>
<td>Pyrolysis temperature of 250°C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ramp of 1°C from r.t. to 120°C, 10°C from 120°C to 250°C</td>
</tr>
<tr>
<td>4-30-24-30-1GUT250NUGT250</td>
<td>Uniform 13C: taurine, Uniform 13C: glucose, Uniform 15N: taurine</td>
<td>Pyrolysis temperature of 250°C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ramp of 1°C throughout the temperature range</td>
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<td>Pyrolysis temperature of 200°C</td>
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<td></td>
<td></td>
<td>Ramp of 1°C throughout the temperature range</td>
</tr>
<tr>
<td>4-30-24-30-14-22 CNT2</td>
<td>Uniform 13C: taurine, Uniform 13C: glucose, Uniform 15N: taurine</td>
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<td></td>
<td>Ramp of 1°C throughout the temperature range</td>
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<td>Pyrolysis temperature of 250°C</td>
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<td>Sample</td>
<td>Taurine 13C:</td>
<td>Temperature of</td>
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<tr>
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<tr>
<td>4-30-1</td>
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<td>4-30-2</td>
<td>Uniform taurine</td>
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Figure 1. TEM and EDS images of a) 4-16-L, b) S mapping of 4-16-L, c) spent 4-16-L and d) S mapping of spent 4-16-L.
Figure 2. EDS elemental mapping of 4-16-L
Figure 3. Spectra of 13C-glucose-labeled samples.
Figure 5. Reaction results of glucose/fructose conversion in THF/water solvent. a) conversions; b) selectivities.

Reaction conditions: Solvent: solvent of THF/water 9:1 (v/v), reaction temperature of 160°C, 2wt% glucose/fructose, 5mg each of Lewis and Bronsted catalyst/g of reaction media.

Figure 6. Recyclability study with fructose as feedstock

Reaction conditions: Solvent: solvent of THF/water 9:1 (v/v), reaction temperature of 160°C, 2wt% fructose, 5mg each of Lewis and Bronsted catalyst/g of reaction media.
Supporting information for
PYROLYZING RENEWABLE SUGAR AND TAURINE ON THE SURFACE OF CARBON NANOTUBE(CNT) AS HETEROGENEOUS CATALYSTS FOR HYDROXYMETHYLFURFURAL(HMF) PRODUCTION

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S Figure 3. TEM and EDS images of a) 4-16-B, b) S mapping of 4-16-B, c) spent 4-16-B and d) S mapping of spent 4-16-B.
S Figure 2. Reaction results of glucose and fructose conversion in DMSO/THF solvent. a) conversions; b) selectivities.

Reaction conditions: Solvent: solvent of THF/DMSO 7:3 (v/v), reaction temperature of 120°C, 2wt% glucose or fructose, various catalyst loading is 5mg catalyst/g of reaction media.
CHAPTER 6. RENEWABLE PRODUCTION OF NYLON-6,6 MONOMERS
FROM BIOMASS-DERIVED 5-HYDROXYMETHYLFURFURAL(HMF)

A paper to be submitted to Catalysis Communications

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6.1 Abstract

We report the catalytic conversion of HMF-derived 1,6-hexanediol(HDO) to adipic acid and hexamethylenediamine (HMD) for nylon-6,6 production. Selective oxidation of HDO to adipic acid in yields of ~90 mol\% was achieved with 1 wt\% Au/C and 3 wt\% Pt/TiO\textsubscript{2} under basic and acidic conditions, respectively. In addition, HDO can undergo oxidative amination to form adiponitrile in selectivity of 66.4mol\% by utilizing a homogeneous iodine-containing organic molecule as oxidant and aqueous ammonia as
nitrogen source. Adiponitrile can be subsequently hydrogenated over a Raney nickel catalyst to HMD in close to quantitative yields.

6.2. Introduction

Replacing petroleum-derived fuels and chemicals with sustainable, biomass-derived feedstocks has been the subject of intensive research for the past decade. Using a “platform chemical” approach analogous to the petroleum refinery, the US Department of Energy has identified 12 biomass-derived molecules as platform molecules which can be subsequently derivatized to a variety of starting materials to support the chemical industry. Amongst all the potential candidates, 5-hydroxymethylfurfural (HMF) has attracted much attention in recent years due to progress on its efficient production using glucose or cellulose as a feedstock. HMF-derived monomers have been suggested to be used in the production of synthetic plastics and other chemicals. Indeed, oxidation of HMF to produce furan dicarboxylic acid (FDCA) with a range of catalyst systems have been demonstrated. Additionally, HMF can also be reduced to diols with or without the furan ring being saturated. Although HMF-derived α,ω-bifunctional molecules are proposed to be a promising replacement to petroleum derived polyethylene terephthalate (PET), challenges still remain with market acceptance such as cost and recyclability.

Herein we set out to develop an integrated catalytic route utilizing HDO as renewable resource to produce nylon 6,6 monomers, adipic acid, and HMD. Nylon 6,6 is a synthetic polymer with an annual production exceeding 4 million metric tons and thus represents a significant target where biorenewable alternatives hold promise. Not only
does the current production method involve using petroleum as a raw material, but this process also contributes significantly to the emission of pollutants such as nitrous oxide and cyanide, as shown in Figure 1. Recently, Buntara et al. reported the synthesis of the nylon 6 monomer camprolactam from renewable HDO using various heterogeneous and homogeneous catalysts. Herein, we report an alternative synthetic pathway to convert HDO to adipic acid and HMD, as depicted in Figure 2. The proposed catalytic routes include two parts: 1) 1,6-hexanediol is catalytically converted with supported Pt, Au nanoparticles in aqueous media with molecular oxygen as an oxidant; 2) 1,6-hexanediol undergoes an oxidative transformation to result in adiponitrile with 1,3-Diiodo-5,5-dimethylhydantoin (DIH) as an oxidant in an aqueous ammonia solution.

6.3. Experiments

6.3.1 Catalyst Preparation

For the diol oxidation reaction, an activated charcoal supported Au catalyst was synthesized by a sol immobilization method. The nanoparticles were formed in an aqueous solution using polyvinyl alcohol as a stabilizer and then reduced by the addition of sodium borohydride. The resulting gold nanoparticles were then deposited on the activated charcoal(AC) support. The 1wt% Au/AC catalyst was then reduced at 573 K for 2h with 100 cm$^3$ min$^{-1}$ of flowing H$_2$ to remove the polyvinyl alcohol from the catalyst. A titania supported Pt catalyst was synthesized by incipient wetness impregnation. The 3wt% Pt/TiO$_2$ catalyst was then calcined at 673 K for 4 h with 100 cm$^3$ min$^{-1}$ of flowing air followed by being reduced at 573 K for 2h with 100 cm$^3$ min$^{-1}$ of flowing H$_2$. The
adiponitrile hydrogenation reaction was catalyzed by a commercially available W.R. Grace Raney® 2400 nickel catalyst and was used as received. The raney-type nickel catalyst was activated before the reaction.

6.3.2 Catalyst Characterization

Metal dispersions of prepared catalysts were determined by H₂ chemisorption using a Micromeritics ASAP 2020 automated adsorption analyzer. Catalysts were heated to 473 K at 4 K min⁻¹ ramp rate under flowing H₂ and reduced for another 2 h. Then, the catalyst samples were evacuated and the temperature was held for 2 h at 473 K, before cooling down to 308 K for analysis with pressure ranging from 10 to 450 Torr. The fraction of surface metal was calculated based on the total amount of H₂ adsorbed with the assumption that stoichiometry of H to Ptₘₕ equals to unity. In order to prepare the Au/AC catalyst sample for TEM analysis, 1 mg sample was dissolved in ethanol and the solution was homogenized for 30 min by sonication. A copper grid was briefly dipped into the solution and the grid was then air dried to evaporate ethanol. A FEI Titan operating at 180 kV and equipped with a Gatan 794 Multi-scan Camera (EFTEM) was used to image the catalyst.

6.3.3 1,6-Hexanediol Oxidation Reaction

Semi-batch HDO oxidation reactions were performed in a 50 cm³ Parr Instrument Company 4592 batch reactor with an inserted 30 cm³ glass liner. In a typical experiment, HDO and catalysts were added to approximately 10 cm³ volume of deionized water followed by addition of sulfuric acid or sodium hydroxide to adjust the solution pH. The
glass liner was then inserted into the Parr reactor, sealed, purged with He and the reactor was then heated to 343 K. 10 bar absolute O\textsubscript{2} was applied to initiate the reaction and throughout the reaction time a constant pressure was maintained by continually feeding O\textsubscript{2}. An aliquot of samples was periodically taken and the solid catalyst was filtered using 0.2 µm pore zide cut-off PTFE filters before being analyzed by a Waters e2695 high pressure liquid chromatograph (HPLC) equipped with RI and UV/Vis detectors. An Aminex HPX-87H column (Bio-Rad) was used under 318 K with 5 mM aqueous H\textsubscript{2}SO\textsubscript{4} solution with mobile phase. 1wt% Au/AC was used to catalyze 1,6-hexanediol oxidation under basic conditions while 3wt% Pt/TiO\textsubscript{2} was tested under acidic conditions.

6.3.4 Direct Oxidative Transformation Of 1,6-Hexanediol To Adiponitrile

The oxidative conversion of 1,6-hexanediol to adiponitrile was carried out in a 10 cm\textsuperscript{3} thick-walled glass reactor (Alltech) sealed with Teflon liners (Fisher). In a typical experiment, an appropriate amount of 1,6-hexanediol and 1,3-Diiodo-5,5-dimethylhydantoin (DIH) were added to 3 mL of 28% aqueous ammonia solution in an Alltech reactor. The reactor was then sealed, wrapped with aluminum foil, and immersed in an oil bath at 60 °C with stirring at 400 rpm. An aliquot of liquid sample was withdrawn periodically to obtain kinetic information and at the end of the reaction the mixture was quenched with H\textsubscript{2}O and saturated aqueous Na\textsubscript{2}SO\textsubscript{3} at 0 °C. A known amount of acetonitrile was introduced to the sample solution as a standard before analysis with an Agilent 7890A gas chromatograph coupled with a mass spectrometer (GC-MS).
6.3.5 Hydrogenation of Adiponitrile to Produce 1,6-Hexanediamine

Hydrogenation of adiponitrile to 1,6-hexanediamine and mono-hydrogenated products was performed in 50 cm$^3$ Parr Instrument batch reactor. After the activation of Raney® 2400 nickel catalyst for 2 h, an appropriate amount of adiponitrile, 50% NaOH additive, and dioxane as a standard were added to a 40 mL ethanol solution. The reactor was pressurized with 500 psi H$_2$ and heated to different temperatures ranging from 80 to 120°C. H$_2$ gas was constantly added to maintain a stable pressure. Samples were removed periodically over 2 h and the catalyst was filtered before analysis with an Agilent 7890A gas chromatograph coupled with a mass spectrometer (GC-MS).

6.4. Results and Discussion

We and others have previously reported that Au or Pt supported on various metal oxides such as TiO$_2$, CeO$_2$ etc. are effective catalysts to convert biomass-derived $\alpha,\omega$-bifunctional molecules such as HMF and 1,6-hexanediol to corresponding di-acids.$^{42,244}$ In this contribution, two types of heterogeneous catalysts, activated charcoal (AC) supported Au nanoparticles (Au/AC) and TiO$_2$ supported Pt nanoparticles (Pt/TiO$_2$) have been examined for the diol oxidation.

First, an activated charcoal(AC) supported Au catalyst was prepared via a sol immobilization method. Au nanoparticles stabilized by polyvinyl alcohol were deposited onto AC, followed by reduction under flowing H$_2$ at 573 K for 2 h. The metal loading
and dispersion of Au nanoparticles ($d_{\text{gold}}$, fraction of exposed surface Au atoms) were determined to be 1.0 wt% and 0.22, respectively. An estimated Au particle size ($1/d_{\text{gold}}$) of ~4.5 nm was obtained through hydrogen chemisorption (H/Au), and gold nanoparticles within this range of diameter were found to be the most active in catalyzing oxidation reaction.²⁴⁵ In line with this interpretation, Figure 3 showed the TEM image of the prepared Au nanoparticles were well dispersed on the support and a statistical Au size analysis result was in agreement with the hydrogen chemisorption results.

To test the catalytic performance of the Au/AC catalyst, an appropriate amount of HDO and catalyst (ratio of substrate to Au was 100:1, mol:mol) were added to a 1 M NaOH aqueous solution under oxygen at 10 bars pressure and 343 K temperature. Excessive base is required because it was found that the adsorbed hydroxide can significantly lower the activation barrier via promoting the deprotonation of alcohol on the surface.²⁴⁶ After 4h, about 97 mol% yield of adipic acid (in a sodium salt form) was obtained at 100% HDO conversion. Although this strategy can produce high yields of adipic acid product, the necessity of neutralizing excessive amount of sodium hydroxide (10:1 M) to recover free acid will complicate the deployment in practice. Therefore, it would be advantageous to develop a process operating under base-free conditions to avoid the need to neutralize the product stream.

In order to realize the aforementioned goal, we synthesized TiO₂ supported Pt catalysts via incipient wetness impregnation method using chloroplatinic acid as the platinum source. The 3 wt% Pt/TiO₂ catalyst was then calcined at 673 K for 4 h in air
followed by reduction at 573 K for another 2 h under flowing H$_2$. Dispersion of surface Pt atoms ($d_{\text{platinum}}$) was determined to be 0.63, which corresponds to an average particle size of about 1.6 nm. The oxidation of HDO with Pt/TiO$_2$ catalyst was then performed under oxygen at 10 bars pressure and 343 K temperature, with no added base. Since 6-hydroxyhexanoic acid and adipic acid will be generated, resulting in the acidification of reaction media as the oxidation reaction proceeds, we adjusted the initial solution value to 2.9 by the addition of sulfuric acid in order to maintain a relatively constant pH value.

The kinetic information of HDO conversion to adipic acid was plotted in Figure 4. The product selectivity of 89 mol% was obtained at complete HDO conversion after 24 h. Although the molar yield and reaction rate under acidic conditions were slightly lower than that produced under basic conditions, the direct production of free diacid is desired due to no further costly purification via ion exchange being required to recover the product. It is also noticed that in addition to the desired product, a significant amount of gaseous CO$_2$ was produced. In order to better understand the reaction path and byproduct formation, we ran experiments using 0.1 M adipic acid and 0.1 M 6-hydroxyhexanoic acid under the same conditions as 1,6-hexanediol. After 24 h of reaction time, carbon selectivity towards CO$_2$ was 16 mol% at 2.9% conversion and 1.8 mol% at 72% conversion for adipic acid and 6-hydroxyhexanoic acid, respectively.

In parallel to the diol oxidation reaction, another effort was undertaken to convert HDO to adiponitrile for the diamine synthesis. The most commonly used procedures to synthesize adiponitrile involve the nucleophilic substitution of appropriate substrates with
inorganic cyanide ions, which is extremely toxic and imposes great environmental concerns. To address this issue, we utilized aqueous ammonia as nitrogen source to aminate HDO. To promote the amination we used DIH, a well-known halogen based oxidant which is effective and less toxic than its Cl or Br derived counterparts.  

Although various primary alcohols have been tested as model compound for this transformation, biomass-derived HDO was yet to be investigated as a starting substrate. In this contribution, HDO was reacted with 4 molar equivalents of DIH as an oxidant in a 28-30 wt% aqueous NH₃ solution at 333 K. As illustrated in Figure 5, a reaction pathway for primary alcohols to produce nitriles with aldehydes and imines as intermediates has been proposed. An adiponitrile selectivity of 66.4mol% was achieved at 64% HDO conversion after 12 h. GC-MS results indicated that at the end of the reaction DIH lost its iodine content, thus subsequent regeneration of DIH is required.

Further catalytic hydrogenation of adiponitrile to produce HMD was also explored to demonstrate the feasibility of proposed diamine production from HDO. A commercial Raney® 2400 nickel catalyst was chosen to catalyze adiponitrile hydrogenation and the procedure was modified based on previous reports. The Raney-type nickel was first activated in an ethanol solution under H₂ for 2 h, followed by the addition of adiponitrile and a small amount of sodium hydroxide to basify the reaction medium. The reaction was carried out at 373 K under 500 psi H₂ pressure. Product distribution versus time was summarized in Figure 6. Under the experimental conditions, HMD was readily formed in high selectivity while adiponitrile was continuously hydrogenated. An HMD selectivity
of ~92 mol% was achieved at full adiponitrile conversion after 2 h. It was noted that reaction temperature played an important role in controlling the product selectivities, a lower selectivity towards HMD was obtained when the reaction temperature was changed to be 353 K.

6.5. Conclusion

In conclusion, an integrated catalytic conversion route utilizing HMF-derived HDO as feedstock for the production of the commodity chemicals adipic acid and HMD was successfully demonstrated. While highly alkaline reaction media was required for the aerobic oxidation of HDO with supported Au catalysts, supported Pt catalysts were shown to be effective in carrying out this reaction in acidic conditions. The latter method is more feasible from an applied perspective for avoiding the subsequent ion exchange process to recover free acid. HDO was also for the first time proposed to undergo oxidative transformation with aqueous ammonia for the production of adiponitrile. Although further techno-economic analysis will be required to evaluate this procedure, the demonstration of technical feasibility is illustrated. Further hydrogenation of produced adiponitrile to HMD is also investigated and high yields were obtained.

Acknowledgments

This work was financially supported by the National Science Foundation under Award No. EEC-0813570.
Reference


Figures

Figure 1. Synthesis pathway of petroleum feedstock derived nylon monomers
Figure 2. Adipic acid and hexamethylenediamine synthesis pathway from biomass platform chemical HMF
Figure 3. TEM image of 1wt% Au/AC catalyst.
Figure 4. Conversion of 1,6-hexanediol to adipic acid at acidic condition with Pt/TiO$_2$ catalyst. Reaction condition: 0.1M 1,6-hexanediol, 1,6-hexanediol to Pt (mol:mol) ratio of 100:1, 10 bar oxygen, pH=2.9, temperature of 343K.
Figure 5. Scheme of 1,6-hexanediol to adiponitrile

a) \( \text{H}_2 \text{C} \equiv \text{OH} \xrightarrow{\text{DIH}} \text{R} \equiv \text{C} \equiv \text{N} \) primary alcohol \( \xrightarrow{\text{DIH}} \) aqueous \( \text{NH}_3 \) nitrile

\[ \text{R} \equiv \text{C} \equiv \text{O} \xrightarrow{\text{NH}_3} \text{R} \equiv \text{C} \equiv \text{NH} \]

\[ \text{R} \equiv \text{C} \equiv \text{N} \xrightarrow{\text{DIH}} \text{R} \equiv \text{C} \equiv \text{NH} \]

b) \( \text{HO} \sim \text{C} \sim \text{OH} \xrightarrow{\text{DIH}} \text{NC} \sim \text{C} \sim \text{CN} \) aqueous \( \text{NH}_3 \)
Figure 6. Product distribution of Raney®2400 nickel catalyzed adiponitrile hydrogenation. Reaction conditions: 0.04mol adiponitrile, 40mL ethanol, 1.9g Raney®2400 nickel catalyst, 0.5g 50wt% NaOH, 500psi hydrogen, temperature of 373K.
CHAPTER 7 CONCLUSIONS AND FUTURE DIRECTIONS

7.1 Conclusions

In summary, the research objective of improving HMF yields from glucose as feedstock has been achieved via two approaches: 1) the exploitation of MCl$_3$-type homogeneous Lewis acidic metal salts as catalysts to effectively isomerize glucose to fructose, followed by a standard Bronsted acid-catalyzed fructose dehydration reaction to HMF; 2) due to the instability of produced HMF under reaction condition, a reaction engineering strategy of separating HMF using an organic solvent has been employed. SBP has been chosen as the extracting solvent in this dissertation work because of its highly effective extraction capability and minimal acids uptake which can ultimately make the downstream processing of produced HMF easier.

Whereas a lot of literature has been reported at the same time or after the publications discussed in this dissertation using various combinations of metal salt catalysts and/or solvent system, there is a lack of systematic studies to deepen the understanding of glucose-fructose-HMF reaction cascade in aqueous media. However, it is extremely important to further investigate and understand the underpinning chemistry and/or catalyst/glucose interactions. For this reason, a series of different groups of metal salts Lewis acids have been chosen for further mechanistic and kinetics study in order to gain the fundamentals of this important dehydration reaction.

With the information regarding reactivities and catalyst/substrate interactions, the effort to immobilize Lewis acidic metals salts on a hydrothermally stable carbon-based catalyst support is also illustrated. In this contribution, solid-state NMR has been utilized
as a powerful tool to understand the carbon content on the surface and guide the synthesis parameters to obtain desired solid acid catalyst. Additionally, TEM/SEM spectroscopies have also been used to characterize the as-made catalysts. Reactions with both glucose and fructose catalyzed by the synthesized solid Lewis acids have been performed with fructose having a high HMF selectivity, in addition to its good recyclability with relatively little catalyst leaching.

In another effort, model HMF-derived chemical, 1,6-hexanediol was also selectively transformed to high-tonnage commodity monomers for nylon synthesis. Supported Pt nanoparticles have shown to be able to catalyse diol oxidation to diacids with molecular oxygen under acidic conditions. DIH based organic molecules, on the other hand, have been shown to be effective in converting diol to dinitrile using ammonia as a source of N element.

7.2 Future Directions

Despite numerous research interest have been focused on HMF production and the a lot of recent literature reporting high HMF yields, the challenge of commercialization of HMF synthesis is still significant. From a scientific point of view, most of the reported results on HMF synthesis are mostly concerned about the HMF yields, in other word, these are thermodynamic aspects of the sugar dehydration reaction. However, in the implementation of a real industrial process, kinetic information is of great concern to develop suitable processes and reactors for such transformations. For this reason, it would be highly urgent for the community to shift some of the effort to truly understand the
reaction mechanism /kinetics, for example, the dissertation provided some insights on this aspect.

Like any other chemical process, feedstock and processing cost would be two major factors in the cost structure. Correspondingly, research effort in pursuit of alternative sources for the feedstock sugar can be promising in addition to understanding the catalytic process to improve the reaction kinetics and/or selectivities. A process utilizing the naturely abundant cellulose as feedstock may have a high chance of successful industrialization.

From a practical perspective, the development of a downstream use or market of HMF is essential to justify the current research effort. In this direction, finding a suitable application of HMF or HMF-derived molecules where their properties can be advantageous compared to petroleum based platform chemicals is highly necessary. In the short term, chemical derivatives of HMF used in medical applications can be a route to demonstrate the biorenewable advantages.